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10-11-00

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PTO/SB/05 (2/98)

Box Sequence

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No.	210121.455C13
First Inventor or Application Identifier	Tongtong Wang
Title	COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER
Express Mail Label No.	EL615232245US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

1. [ ] General Authorization Form & Fee Transmittal *(Submit an original and a duplicate for fee processing)*
2. [x] Specification [Total Pages] 161 *(preferred arrangement set forth below)*
   - Descriptive Title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [x] Drawing(s) *(35 USC 113)* [Total Sheets] 3
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. [ ] Incorporation By Reference *(useable if box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program *(Appendix)*
7. Nucleotide and Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [x] Computer-Readable Copy
   b. [x] Paper Copy (identical to computer copy)
   c. [x] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [x] Return Receipt Postcard
14. [ ] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [x] Other: Certificate of Express Mail

17. **If a CONTINUING APPLICATION,** *check appropriate box and supply the requisite information below and in a preliminary amendment*

[ ] Continuation [ ] Divisional [x] Continuation-In-Part (CIP) of prior Application No.: **09/not assigned**

Prior application information: Examiner **not assigned** *Group / Art Unit* **not assigned**

[ ] Claims the benefit of Provisional Application No.

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Respectfully submitted,

TYPED or PRINTED NAME Jane E. R. Potter REGISTRATION NO. 33,332

SIGNATURE Jane E R Potter Date October 9, 2000

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

JC892 U.S. PTO
09/685696
10/09/00

Applicants : Tongtong Wang, Medina, WA; Liqun Fan, Bellevue, WA; Michael D. Kalos, Seattle, WA; Chaitanya S. Bangur, Seattle, WA; Nancy A. Hosken, Seattle, WA; Gary R. Fanger, Mill Creek, WA; Samuel X. Li; Redmond WA; Aijun Wang, Issaquah, WA; Yasir A. W. Skeiky, Seattle, WA; Robert A. Henderson, Edmonds, WA; Patricia D. McNeill, Des Moines, WA

Filed : October 9, 2000

For : COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

Docket No. : 210121.455C13

Date : October 9, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Assistant Commissioner for Patents:

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Respectfully submitted,

Seed Intellectual Property Law Group PLLC

Jeanette West

Steve Plante/Jeanette West/Susan Johnson

JEP:sds
Enclosures:
Postcard
Form PTO/SB/05
Specification, Claims, Abstract (161 pages)
3 Sheets Drawings (Figs. 1-3)
Sequence Listing (187 pages)
Declaration for Sequence Listing
Diskette for Sequence Listing

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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is related to U.S. Patent Application Nos. _____, filed September 26, 2000; 09/643,597, filed August 21, 2000; 09/630,940 filed August 2, 2000; 09/606,421 filed June 28, 2000; 09/542,615 filed April 4, 2000; 09/510,376 filed February 22, 2000; 09/480,884 filed January 10, 2000; 09/476,496 filed December 30, 1999; 09/466,396 filed December 17, 1999; 09/285,479 filed April 2, 1999; 09/221,107 filed December 22, 1998; 09/123,912 filed July 27, 1998; 09/040,802 filed March 18, 1998; each a CIP of the previous application and each pending; and PCT Nos. US99/05798 filed March 17, 1999, published, and US00/08896 filed April 4, 2000, pending; all incorporated by reference herein.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. The invention is more specifically related to polypeptides comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of lung cancer, and for the diagnosis and monitoring of such cancers.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as lung cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347 and 349; (b) variants of a sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347 and 349; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in

any one of SEQ ID NO: 152, 155, 156, 165, 166, 169, 170, 172, 174, 176, 226-252, 338-344 and 346, and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines for prophylactic or therapeutic use are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a lung tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above, and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Determined T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells determined from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide;

and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as

recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE FIGURES AND SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for LST-S1-2

SEQ ID NO: 2 is the determined cDNA sequence for LST-S1-28

SEQ ID NO: 3 is the determined cDNA sequence for LST-S1-90

SEQ ID NO: 4 is the determined cDNA sequence for LST-S1-144

SEQ ID NO: 5 is the determined cDNA sequence for LST-S1-133

SEQ ID NO: 6 is the determined cDNA sequence for LST-S1-169

SEQ ID NO: 7 is the determined cDNA sequence for LST-S2-6

SEQ ID NO: 8 is the determined cDNA sequence for LST-S2-11

SEQ ID NO: 9 is the determined cDNA sequence for LST-S2-17

SEQ ID NO: 10 is the determined cDNA sequence for LST-S2-25

SEQ ID NO: 11 is the determined cDNA sequence for LST-S2-39

SEQ ID NO: 12 is a first determined cDNA sequence for LST-S2-43

SEQ ID NO: 13 is a second determined cDNA sequence for LST-S2-43

SEQ ID NO: 14 is the determined cDNA sequence for LST-S2-65

SEQ ID NO: 15 is the determined cDNA sequence for LST-S2-68

SEQ ID NO: 16 is the determined cDNA sequence for LST-S2-72

SEQ ID NO: 17 is the determined cDNA sequence for LST-S2-74

SEQ ID NO: 18 is the determined cDNA sequence for LST-S2-103

SEQ ID NO: 19 is the determined cDNA sequence for LST-S2-N1-1F

SEQ ID NO: 20 is the determined cDNA sequence for LST-S2-N1-2A

SEQ ID NO: 21 is the determined cDNA sequence for LST-S2-N1-4H

SEQ ID NO: 22 is the determined cDNA sequence for LST-S2-N1-5A

SEQ ID NO: 23 is the determined cDNA sequence for LST-S2-N1-6B

SEQ ID NO: 24 is the determined cDNA sequence for LST-S2-N1-7B

SEQ ID NO: 25 is the determined cDNA sequence for LST-S2-N1-7H

SEQ ID NO: 26 is the determined cDNA sequence for LST-S2-N1-8A

SEQ ID NO: 27 is the determined cDNA sequence for LST-S2-N1-8D

SEQ ID NO: 28 is the determined cDNA sequence for LST-S2-N1-9A

SEQ ID NO: 29 is the determined cDNA sequence for LST-S2-N1-9E

SEQ ID NO: 30 is the determined cDNA sequence for LST-S2-N1-10A

SEQ ID NO: 31 is the determined cDNA sequence for LST-S2-N1-10G

SEQ ID NO: 32 is the determined cDNA sequence for LST-S2-N1-11A

SEQ ID NO: 33 is the determined cDNA sequence for LST-S2-N1-12C

SEQ ID NO: 34 is the determined cDNA sequence for LST-S2-N1-12E

SEQ ID NO: 35 is the determined cDNA sequence for LST-S2-B1-3D

SEQ ID NO: 36 is the determined cDNA sequence for LST-S2-B1-6C

SEQ ID NO: 37 is the determined cDNA sequence for LST-S2-B1-5D

SEQ ID NO: 38 is the determined cDNA sequence for LST-S2-B1-5F

SEQ ID NO: 39 is the determined cDNA sequence for LST-S2-B1-6G

SEQ ID NO: 40 is the determined cDNA sequence for LST-S2-B1-8A

SEQ ID NO: 41 is the determined cDNA sequence for LST-S2-B1-8D

SEQ ID NO: 42 is the determined cDNA sequence for LST-S2-B1-10A

SEQ ID NO: 43 is the determined cDNA sequence for LST-S2-B1-9B

SEQ ID NO: 44 is the determined cDNA sequence for LST-S2-B1-9F

SEQ ID NO: 45 is the determined cDNA sequence for LST-S2-B1-12D

SEQ ID NO: 46 is the determined cDNA sequence for LST-S2-I2-2B

SEQ ID NO: 47 is the determined cDNA sequence for LST-S2-I2-5F

SEQ ID NO: 48 is the determined cDNA sequence for LST-S2-I2-6B

SEQ ID NO: 49 is the determined cDNA sequence for LST-S2-I2-7F

SEQ ID NO: 50 is the determined cDNA sequence for LST-S2-I2-8G

SEQ ID NO: 51 is the determined cDNA sequence for LST-S2-I2-9E

SEQ ID NO: 52 is the determined cDNA sequence for LST-S2-I2-12B

SEQ ID NO: 53 is the determined cDNA sequence for LST-S2-H2-2C

SEQ ID NO: 54 is the determined cDNA sequence for LST-S2-H2-1G

SEQ ID NO: 55 is the determined cDNA sequence for LST-S2-H2-4G

SEQ ID NO: 56 is the determined cDNA sequence for LST-S2-H2-3H

SEQ ID NO: 57 is the determined cDNA sequence for LST-S2-H2-5G

SEQ ID NO: 58 is the determined cDNA sequence for LST-S2-H2-9B

SEQ ID NO: 59 is the determined cDNA sequence for LST-S2-H2-10H

SEQ ID NO: 60 is the determined cDNA sequence for LST-S2-H2-12D

SEQ ID NO: 61 is the determined cDNA sequence for LST-S3-2

SEQ ID NO: 62 is the determined cDNA sequence for LST-S3-4

SEQ ID NO: 63 is the determined cDNA sequence for LST-S3-7

SEQ ID NO: 64 is the determined cDNA sequence for LST-S3-8

SEQ ID NO: 65 is the determined cDNA sequence for LST-S3-12

SEQ ID NO: 66 is the determined cDNA sequence for LST-S3-13

SEQ ID NO: 67 is the determined cDNA sequence for LST-S3-14

SEQ ID NO: 68 is the determined cDNA sequence for LST-S3-16

SEQ ID NO: 69 is the determined cDNA sequence for LST-S3-21

SEQ ID NO: 70 is the determined cDNA sequence for LST-S3-22

SEQ ID NO: 71 is the determined cDNA sequence for LST-S1-7

SEQ ID NO: 72 is the determined cDNA sequence for LST-S1-A-1E

SEQ ID NO: 73 is the determined cDNA sequence for LST-S1-A-1G

SEQ ID NO: 74 is the determined cDNA sequence for LST-S1-A-3E

SEQ ID NO: 75 is the determined cDNA sequence for LST-S1-A-4E

SEQ ID NO: 76 is the determined cDNA sequence for LST-S1-A-6D

SEQ ID NO: 77 is the determined cDNA sequence for LST-S1-A-8D

SEQ ID NO: 78 is the determined cDNA sequence for LST-S1-A-10A

SEQ ID NO: 79 is the determined cDNA sequence for LST-S1-A-10C

SEQ ID NO: 80 is the determined cDNA sequence for LST-S1-A-9D

SEQ ID NO: 81 is the determined cDNA sequence for LST-S1-A-10D

SEQ ID NO: 82 is the determined cDNA sequence for LST-S1-A-9H

SEQ ID NO: 83 is the determined cDNA sequence for LST-S1-A-11D

SEQ ID NO: 84 is the determined cDNA sequence for LST-S1-A-12D

SEQ ID NO: 85 is the determined cDNA sequence for LST-S1-A-11E

SEQ ID NO: 86 is the determined cDNA sequence for LST-S1-A-12E

SEQ ID NO: 87 is the determined cDNA sequence for L513S (T3).

SEQ ID NO: 88 is the determined cDNA sequence for L513S contig 1.

SEQ ID NO: 89 is a first determined cDNA sequence for L514S.

SEQ ID NO: 90 is a second determined cDNA sequence for L514S.

SEQ ID NO: 91 is a first determined cDNA sequence for L516S.

SEQ ID NO: 92 is a second determined cDNA sequence for L516S.

SEQ ID NO: 93 is the determined cDNA sequence for L517S.

SEQ ID NO: 94 is the extended cDNA sequence for LST-S1-169 (also known as L519S).

SEQ ID NO: 95 is a first determined cDNA sequence for L520S.

SEQ ID NO: 96 is a second determined cDNA sequence for L520S.

SEQ ID NO: 97 is a first determined cDNA sequence for L521S.

SEQ ID NO: 98 is a second determined cDNA sequence for L521S.

SEQ ID NO: 99 is the determined cDNA sequence for L522S.

SEQ ID NO: 100 is the determined cDNA sequence for L523S.

SEQ ID NO: 101 is the determined cDNA sequence for L524S.

SEQ ID NO: 102 is the determined cDNA sequence for L525S.

SEQ ID NO: 103 is the determined cDNA sequence for L526S.

SEQ ID NO: 104 is the determined cDNA sequence for L527S.

SEQ ID NO: 105 is the determined cDNA sequence for L528S.

SEQ ID NO: 106 is the determined cDNA sequence for L529S.

SEQ ID NO: 107 is a first determined cDNA sequence for L530S.

SEQ ID NO: 108 is a second determined cDNA sequence for L530S.

SEQ ID NO: 109 is the determined full-length cDNA sequence for L531S short form

SEQ ID NO: 110 is the predicted amino acid sequence encoded by SEQ ID NO: 109.

SEQ ID NO: 111 is the determined full-length cDNA sequence for L531S long form

SEQ ID NO: 112 is the predicted amino acid sequence encoded by SEQ ID NO: 111.

SEQ ID NO: 113 is the determined full-length cDNA sequence for L520S.

SEQ ID NO: 114 is the predicted amino acid sequence encoded by SEQ ID NO: 113.

SEQ ID NO: 115 is the determined cDNA sequence for contig 1.

SEQ ID NO: 116 is the determined cDNA sequence for contig 3.

SEQ ID NO: 117 is the determined cDNA sequence for contig 4.

SEQ ID NO: 118 is the determined cDNA sequence for contig 5.

SEQ ID NO: 119 is the determined cDNA sequence for contig 7.

SEQ ID NO: 120 is the determined cDNA sequence for contig 8.

SEQ ID NO: 121 is the determined cDNA sequence for contig 9.

SEQ ID NO: 122 is the determined cDNA sequence for contig 10.

SEQ ID NO: 123 is the determined cDNA sequence for contig 12.

SEQ ID NO: 124 is the determined cDNA sequence for contig 11.

SEQ ID NO: 125 is the determined cDNA sequence for contig 13 (also known as L761P).

SEQ ID NO: 126 is the determined cDNA sequence for contig 15.

SEQ ID NO: 127 is the determined cDNA sequence for contig 16.

SEQ ID NO: 128 is the determined cDNA sequence for contig 17.

SEQ ID NO: 129 is the determined cDNA sequence for contig 19.

SEQ ID NO: 130 is the determined cDNA sequence for contig 20.

SEQ ID NO: 131 is the determined cDNA sequence for contig 22.

SEQ ID NO: 132 is the determined cDNA sequence for contig 24.

SEQ ID NO: 133 is the determined cDNA sequence for contig 29.

SEQ ID NO: 134 is the determined cDNA sequence for contig 31.

SEQ ID NO: 135 is the determined cDNA sequence for contig 33.

SEQ ID NO: 136 is the determined cDNA sequence for contig 38.

SEQ ID NO: 137 is the determined cDNA sequence for contig 39.

SEQ ID NO: 138 is the determined cDNA sequence for contig 41.

SEQ ID NO: 139 is the determined cDNA sequence for contig 43.

SEQ ID NO: 140 is the determined cDNA sequence for contig 44.

SEQ ID NO: 141 is the determined cDNA sequence for contig 45.

SEQ ID NO: 142 is the determined cDNA sequence for contig 47.

SEQ ID NO: 143 is the determined cDNA sequence for contig 48.

SEQ ID NO: 144 is the determined cDNA sequence for contig 49.

SEQ ID NO: 145 is the determined cDNA sequence for contig 50.

SEQ ID NO: 146 is the determined cDNA sequence for contig 53.

SEQ ID NO: 147 is the determined cDNA sequence for contig 54.

SEQ ID NO: 148 is the determined cDNA sequence for contig 56.

SEQ ID NO: 149 is the determined cDNA sequence for contig 57.

SEQ ID NO: 150 is the determined cDNA sequence for contig 58.

SEQ ID NO: 151 is the full-length cDNA sequence for L530S.

SEQ ID NO: 152 is the amino acid sequence encoded by SEQ ID NO: 151

SEQ ID NO: 153 is the full-length cDNA sequence of a first variant of L514S

SEQ ID NO: 154 is the full-length cDNA sequence of a second variant of L514S

SEQ ID NO: 155 is the amino acid sequence encoded by SEQ ID NO: 153.

SEQ ID NO: 156 is the amino acid sequence encoded by SEQ ID NO: 154.

SEQ ID NO: 157 is the determined cDNA sequence for contig 59.

SEQ ID NO: 158 is the full-length cDNA sequence for L763P (also referred to as contig 22).

SEQ ID NO: 159 is the amino acid sequence encoded by SEQ ID NO: 158.

SEQ ID NO: 160 is the full-length cDNA sequence for L762P (also referred to as contig 17).

SEQ ID NO: 161 is the amino acid sequence encoded by SEQ ID NO: 160.

SEQ ID NO: 162 is the determined cDNA sequence for L515S.

SEQ ID NO: 163 is the full-length cDNA sequence of a first variant of L524S.

SEQ ID NO: 164 is the full-length cDNA sequence of a second variant of L524S.

SEQ ID NO: 165 is the amino acid sequence encoded by SEQ ID NO: 163.

SEQ ID NO: 166 is the amino acid sequence encoded by SEQ ID NO: 164.

SEQ ID NO: 167 is the full-length cDNA sequence of a first variant of L762P.

SEQ ID NO: 168 is the full-length cDNA sequence of a second variant of L762P.

SEQ ID NO: 169 is the amino acid sequence encoded by SEQ ID NO: 167.

SEQ ID NO: 170 is the amino acid sequence encoded by SEQ ID NO: 168.

SEQ ID NO: 171 is the full-length cDNA sequence for L773P (also referred to as contig 56).

SEQ ID NO: 172 is the amino acid sequence encoded by SEQ ID NO: 171.

SEQ ID NO: 173 is an extended cDNA sequence for L519S.

SEQ ID NO: 174 is the predicted amino acid sequence encoded by SEQ ID NO: 174.

SEQ ID NO: 175 is the full-length cDNA sequence for L523S.

SEQ ID NO: 176 is the predicted amino acid sequence encoded by SEQ ID NO: 175.

SEQ ID NO: 177 is the determined cDNA sequence for LST-sub5-7A.

SEQ ID NO: 178 is the determined cDNA sequence for LST-sub5-8G.

SEQ ID NO: 179 is the determined cDNA sequence for LST-sub5-8H.

SEQ ID NO: 180 is the determined cDNA sequence for LST-sub5-10B.

SEQ ID NO: 181 is the determined cDNA sequence for LST-sub5-10H.

SEQ ID NO: 182 is the determined cDNA sequence for LST-sub5-12B.

SEQ ID NO: 183 is the determined cDNA sequence for LST-sub5-11C.

SEQ ID NO: 184 is the determined cDNA sequence for LST-sub6-1c.

SEQ ID NO: 185 is the determined cDNA sequence for LST-sub6-2f.

SEQ ID NO: 186 is the determined cDNA sequence for LST-sub6-2G.

SEQ ID NO: 187 is the determined cDNA sequence for LST-sub6-4d.

SEQ ID NO: 188 is the determined cDNA sequence for LST-sub6-4e.

SEQ ID NO: 189 is the determined cDNA sequence for LST-sub6-4f.

SEQ ID NO: 190 is the determined cDNA sequence for LST-sub6-3h.

SEQ ID NO: 191 is the determined cDNA sequence for LST-sub6-5d.

SEQ ID NO: 192 is the determined cDNA sequence for LST-sub6-5h.

SEQ ID NO: 193 is the determined cDNA sequence for LST-sub6-6h.

SEQ ID NO: 194 is the determined cDNA sequence for LST-sub6-7a.

SEQ ID NO: 195 is the determined cDNA sequence for LST-sub6-8a.

SEQ ID NO: 196 is the determined cDNA sequence for LST-sub6-7d.

SEQ ID NO: 197 is the determined cDNA sequence for LST-sub6-7e.

SEQ ID NO: 198 is the determined cDNA sequence for LST-sub6-8e.

SEQ ID NO: 199 is the determined cDNA sequence for LST-sub6-7g.

SEQ ID NO: 200 is the determined cDNA sequence for LST-sub6-9f.

SEQ ID NO: 201 is the determined cDNA sequence for LST-sub6-9h.

SEQ ID NO: 202 is the determined cDNA sequence for LST-sub6-11b.

SEQ ID NO: 203 is the determined cDNA sequence for LST-sub6-11c.

SEQ ID NO: 204 is the determined cDNA sequence for LST-sub6-12c.

SEQ ID NO: 205 is the determined cDNA sequence for LST-sub6-12e.

SEQ ID NO: 206 is the determined cDNA sequence for LST-sub6-12f.

SEQ ID NO: 207 is the determined cDNA sequence for LST-sub6-11g.

SEQ ID NO: 208 is the determined cDNA sequence for LST-sub6-12g.

SEQ ID NO: 209 is the determined cDNA sequence for LST-sub6-12h.

SEQ ID NO: 210 is the determined cDNA sequence for LST-sub6-II-1a.

SEQ ID NO: 211 is the determined cDNA sequence for LST-sub6-II-2b.

SEQ ID NO: 212 is the determined cDNA sequence for LST-sub6-II-2g.

SEQ ID NO: 213 is the determined cDNA sequence for LST-sub6-II-1h.

SEQ ID NO: 214 is the determined cDNA sequence for LST-sub6-II-4a.

SEQ ID NO: 215 is the determined cDNA sequence for LST-sub6-II-4b.

SEQ ID NO: 216 is the determined cDNA sequence for LST-sub6-II-3e.

SEQ ID NO: 217 is the determined cDNA sequence for LST-sub6-II-4f.

SEQ ID NO: 218 is the determined cDNA sequence for LST-sub6-II-4g.

SEQ ID NO: 219 is the determined cDNA sequence for LST-sub6-II-4h.

SEQ ID NO: 220 is the determined cDNA sequence for LST-sub6-II-5c.

SEQ ID NO: 221 is the determined cDNA sequence for LST-sub6-II-5e.

SEQ ID NO: 222 is the determined cDNA sequence for LST-sub6-II-6f.

SEQ ID NO: 223 is the determined cDNA sequence for LST-sub6-II-5g.

SEQ ID NO: 224 is the determined cDNA sequence for LST-sub6-II-6g.

SEQ ID NO: 225 is the amino acid sequence for L528S.

SEQ ID NO: 226-251 are synthetic peptides derived from L762P.

SEQ ID NO: 252 is the expressed amino acid sequence of L514S.

SEQ ID NO: 253 is the DNA sequence corresponding to SEQ ID NO: 252.

SEQ ID NO: 254 is the DNA sequence of a L762P expression construct.

SEQ ID NO: 255 is the determined cDNA sequence for clone 23785.

SEQ ID NO: 256 is the determined cDNA sequence for clone 23786.

SEQ ID NO: 257 is the determined cDNA sequence for clone 23788.

SEQ ID NO: 258 is the determined cDNA sequence for clone 23790.

SEQ ID NO: 259 is the determined cDNA sequence for clone 23793.

SEQ ID NO: 260 is the determined cDNA sequence for clone 23794.

SEQ ID NO: 261 is the determined cDNA sequence for clone 23795.

SEQ ID NO: 262 is the determined cDNA sequence for clone 23796.

SEQ ID NO: 263 is the determined cDNA sequence for clone 23797.

SEQ ID NO: 264 is the determined cDNA sequence for clone 23798.

SEQ ID NO: 265 is the determined cDNA sequence for clone 23799.

SEQ ID NO: 266 is the determined cDNA sequence for clone 23800.

SEQ ID NO: 267 is the determined cDNA sequence for clone 23802.

SEQ ID NO: 268 is the determined cDNA sequence for clone 23803.

SEQ ID NO: 269 is the determined cDNA sequence for clone 23804.

SEQ ID NO: 270 is the determined cDNA sequence for clone 23805.

SEQ ID NO: 271 is the determined cDNA sequence for clone 23806.

SEQ ID NO: 272 is the determined cDNA sequence for clone 23807.

SEQ ID NO: 273 is the determined cDNA sequence for clone 23808.

SEQ ID NO: 274 is the determined cDNA sequence for clone 23809.

SEQ ID NO: 275 is the determined cDNA sequence for clone 23810.

SEQ ID NO: 276 is the determined cDNA sequence for clone 23811.

SEQ ID NO: 277 is the determined cDNA sequence for clone 23812.

SEQ ID NO: 278 is the determined cDNA sequence for clone 23813.

SEQ ID NO: 279 is the determined cDNA sequence for clone 23815.

SEQ ID NO: 280 is the determined cDNA sequence for clone 25298.

SEQ ID NO: 281 is the determined cDNA sequence for clone 25299.

SEQ ID NO: 282 is the determined cDNA sequence for clone 25300.

SEQ ID NO: 283 is the determined cDNA sequence for clone 25301

SEQ ID NO: 284 is the determined cDNA sequence for clone 25304

SEQ ID NO: 285 is the determined cDNA sequence for clone 25309.

SEQ ID NO: 286 is the determined cDNA sequence for clone 25312.

SEQ ID NO: 287 is the determined cDNA sequence for clone 25317.

SEQ ID NO: 288 is the determined cDNA sequence for clone 25321.

SEQ ID NO: 289 is the determined cDNA sequence for clone 25323.

SEQ ID NO: 290 is the determined cDNA sequence for clone 25327.

SEQ ID NO: 291 is the determined cDNA sequence for clone 25328.

SEQ ID NO: 292 is the determined cDNA sequence for clone 25332.

SEQ ID NO: 293 is the determined cDNA sequence for clone 25333.

SEQ ID NO: 294 is the determined cDNA sequence for clone 25336.

SEQ ID NO: 295 is the determined cDNA sequence for clone 25340.

SEQ ID NO: 296 is the determined cDNA sequence for clone 25342.

SEQ ID NO: 297 is the determined cDNA sequence for clone 25356.

SEQ ID NO: 298 is the determined cDNA sequence for clone 25357.

SEQ ID NO: 299 is the determined cDNA sequence for clone 25361.

SEQ ID NO: 300 is the determined cDNA sequence for clone 25363.

SEQ ID NO: 301 is the determined cDNA sequence for clone 25397.

SEQ ID NO: 302 is the determined cDNA sequence for clone 25402.

SEQ ID NO: 303 is the determined cDNA sequence for clone 25403.

SEQ ID NO: 304 is the determined cDNA sequence for clone 25405.

SEQ ID NO: 305 is the determined cDNA sequence for clone 25407.

SEQ ID NO: 306 is the determined cDNA sequence for clone 25409.

SEQ ID NO: 307 is the determined cDNA sequence for clone 25396.

SEQ ID NO: 308 is the determined cDNA sequence for clone 25414.

SEQ ID NO: 309 is the determined cDNA sequence for clone 25410.

SEQ ID NO: 310 is the determined cDNA sequence for clone 25406.

SEQ ID NO: 311 is the determined cDNA sequence for clone 25306.

SEQ ID NO: 312 is the determined cDNA sequence for clone 25362.

SEQ ID NO: 313 is the determined cDNA sequence for clone 25360.

SEQ ID NO: 314 is the determined cDNA sequence for clone 25398.

SEQ ID NO: 315 is the determined cDNA sequence for clone 25355.

SEQ ID NO: 316 is the determined cDNA sequence for clone 25351.

SEQ ID NO: 317 is the determined cDNA sequence for clone 25331.

SEQ ID NO: 318 is the determined cDNA sequence for clone 25338.

SEQ ID NO: 319 is the determined cDNA sequence for clone 25335.

SEQ ID NO: 320 is the determined cDNA sequence for clone 25329.

SEQ ID NO: 321 is the determined cDNA sequence for clone 25324.

SEQ ID NO: 322 is the determined cDNA sequence for clone 25322.

SEQ ID NO: 323 is the determined cDNA sequence for clone 25319.

SEQ ID NO: 324 is the determined cDNA sequence for clone 25316.

SEQ ID NO: 325 is the determined cDNA sequence for clone 25311.

SEQ ID NO: 326 is the determined cDNA sequence for clone 25310.

SEQ ID NO: 327 is the determined cDNA sequence for clone 25302.

SEQ ID NO: 328 is the determined cDNA sequence for clone 25315.

SEQ ID NO: 329 is the determined cDNA sequence for clone 25308.

SEQ ID NO: 330 is the determined cDNA sequence for clone 25303.

SEQ ID NO: 331-337 are the cDNA sequences of isoforms of the p53 tumor suppressor homologue, p63 (also referred to as L530S).

SEQ ID NO: 338-344 are the amino acid sequences encoded by SEQ ID NO: 331-337, respectively.

SEQ ID NO: 345 is a second cDNA sequence for the antigen L763P.

SEQ ID NO: 346 is the amino acid sequence encoded by the sequence of SEQ ID NO: 345.

SEQ ID NO: 347 is a determined full-length cDNA sequence for L523S.

SEQ ID NO: 348 is the predicted amino acid sequence encoded by SEQ ID NO: 347.

SEQ ID NO: 349 is the cDNA sequence encoding the N-terminal portion of L773P.

SEQ ID NO: 350 is the amino acid sequence of the N-terminal portion of L773P.

SEQ ID NO: 351 is polynucleotide sequence encoding the fusion of Ral2 and the N-terminal portion of L763P

SEQ ID NO: 352 is the amino acid sequence of the fusion of Ral2 and the N-terminal portion of L763P

SEQ ID NO: 353 is polynucleotide sequence encoding the fusion of Ral2 and the C-terminal portion of L763P

SEQ ID NO: 354 is the amino acid sequence of the fusion of Ral2 and the C-terminal portion of L763P

SEQ ID NO:355 is a primer.

SEQ ID NO:356 is a primer.

SEQ ID NO:357 is the protein sequence of expressed recombinant L762P.

SEQ ID NO:358 is the DNA sequence of expressed recombinant L762P.

SEQ ID NO:359 is a primer.

SEQ ID NO:360 is a primer.

SEQ ID NO:361 is the protein sequence of expressed recombinant L773P A.

SEQ ID NO:362 is the DNA sequence of expressed recombinant L773P A.

SEQ ID NO:363 is an epitope derived from clone L773P polypeptide.

SEQ ID NO:364 is a polynucleotide encoding the polypeptide of SEQ ID NO:363.

SEQ ID NO:365 is an epitope derived from clone L773P polypeptide.

SEQ ID NO:366 is a polynucleotide encoding the polypeptide of SEQ ID NO:365.

SEQ ID NO:367 is an epitope consisting of amino acids 571-590 of SEQ ID NO:161, clone L762.

SEQ ID NO:368 is the full-length DNA sequence for contig 13 (SEQ ID NO:125), also referred to as L761P.

SEQ ID NO:369 is the protein sequence encoded by the DNA sequence of SEQ ID NO:368.

SEQ ID NO:370 is an L762P DNA sequence from nucleotides 2071-2130.

SEQ ID NO:371 is an L762P DNA sequence from nucleotides 1441-1500.

SEQ ID NO:372 is an L762P DNA sequence from nucleotides 1936-1955.

SEQ ID NO:373 is an L762P DNA sequence from nucleotides 2620-2679.

SEQ ID NO:374 is an L762P DNA sequence from nucleotides 1801-1860.

SEQ ID NO:375 is an L762P DNA sequence from nucleotides 1531-1591.

SEQ ID NO:376 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO: 373.

SEQ ID NO:377 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO: 370.

SEQ ID NO:378 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO: 372.

SEQ ID NO:379 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO: 374.

SEQ ID NO:380 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO: 371.

SEQ ID NO:381 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO: 375.

Figure 1 shows the sequences of eleven L773P peptides.

Figure 2 shows that three CD4T cell lines (3C, 6G and 12B) recognized the appropriate L773P peptide as well as recombinant L773P and L773PA.

Figure 3 shows that individual CD4 T cell lines demonstrated cytokine release (IFN gamma) in response to the stimulating peptide but not the control peptide.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as lung cancer. The compositions described herein may include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.,* T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a lung tumor protein or a variant thereof. A "lung tumor protein" is a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is

complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery human lung tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154,157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347 and 349.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NO:1-109, 111, 113, 115-151, 153, 154,157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347 and 349, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO:110, 112, 114, 152, 155, 156, 159, 161, 165, 166, 169, 170, 172, 174, 176, 225, 252, 338-344, 346, 348, and 350, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human lung cancer.

POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons

between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0

algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.,* gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.,* the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like,

(including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Any polynucleotide that encodes a lung tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a lung tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a lung tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-

stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately

depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO:1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347 and 349, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene

fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to

the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia *et al.*, *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom *et al.*, *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker *et al.*, *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to

generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it

may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press,

Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of

interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J. 3*:1671-1680; Broglie, R. *et al.* (1984) *Science 224*:838-843; and Winter, J. *et al.* (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in

Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. *et al.* (1994) *Proc. Natl. Acad. Sci. 91* :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. *et al.* (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. *et al.* (1980) *Proc. Natl. Acad. Sci. 77*:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol. 150*:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been

described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci. 85*:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol. 55*:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological

Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the

encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif. 3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol. 12*:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc. 85*:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself,

and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR™, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide

5'-[α-thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (*e.g.,* biotin) and/or a detector moiety (*e.g.,* enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.,* 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to

make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

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TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been

assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (–0.4); threonine (–0.7); serine (–0.8); tryptophan (–0.9); tyrosine (–1.3); proline (–1.6); histidine (–3.2); glutamate (–3.5); glutamine (–3.5); aspartate (–3.5); asparagine (–3.5); lysine (–3.9); and arginine (–4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (–0.4); proline (–0.5 ± 1); alanine (–0.5); histidine (–0.5); cysteine (–1.0); methionine (–1.3); valine (–1.5); leucine (–1.8); isoleucine (–1.8); tyrosine (–2.3); phenylalanine (–2.5); tryptophan (–3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their

hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety or well known approaches, several of which are outlined below for the purpose of illustration.

1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because

adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5′-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is

dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*, 10^9-10^{11} plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant

adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5′ and 3′ ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene

transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs (FIG. 2). There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral

promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive

properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell

membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for

polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal $GABA_A$ receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m, binding energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.,* 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et*

al., 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-*ras*, c-*fos* and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to

a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as

one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*, 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold into

the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5′-end, and phosphoramidites at the 3′-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2′-amino, 2′-C-allyl, 2′-flouro, 2′-o-methyl, 2′-H (for a review see *e.g.,* Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be

administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993; L'Huillier *et al.*, 1992; Lisziewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter,

decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific

functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3′ to 5′ polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence

specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.,* 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification (Orum *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO:110, 112, 114, 152, 155, 156, 159, 161, 165, 166, 169, 170, 172, 174, 176, 225, 226-251, 252, 338-344, 346, 348 and 350, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO:1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347 and 349, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO:110, 112, 114, 152, 155, 156, 159, 161, 165, 166, 169, 170, 172, 174, 176, 225, 226-251, 252, 338-344, 346, 348 and 350.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal

deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and

evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral

amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene 40*:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute *et al.* *New Engl. J. Med.*, *336*:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two

separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of

recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* *6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the

ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker

group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter *et al.*), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn *et al.*), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler *et al.*).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as

albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato *et al.*), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih *et al.*). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide.

Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res.* *54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan *et al.*, Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without

the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.,* oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup of elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active

compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.,* glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility,

pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.,* in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed

herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran *et al.*, 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μm.

Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by

large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those

organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be are easily made, as described (Couvreur *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

VACCINES

In certain preferred embodiments of the present invention, vaccines are provided. The vaccines will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes

(into which the compound is incorporated; *see e.g.,* Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

Illustrative vaccines may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ.* As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.,* vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch *et al., Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner *et al., Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner *et al., Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld *et al., Science 252*:431-434, 1991; Kolls *et al., Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler *et al., Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman *et al., Circulation 88*:2838-2848, 1993; and Guzman *et al., Cir. Res. 73*:1202-1207, 1993.

Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer *et al.*, *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that a vaccine may comprise both a polynucleotide and a polypeptide component. Such vaccines may provide for an enhanced immune response.

It will be apparent that a vaccine may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the vaccine compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-

type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science 273*:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.,* a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes *et al.*, *Vaccine 14*:1429-1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.,* a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.,* U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be

immunologically compatible with the receiver (*i.e.,* matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel *et al.*, *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC

with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi *et al.*, *Immunology and cell Biology 75*:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Vaccines and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a vaccine or pharmaceutical composition may be stored in a

freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as lung cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages)

expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever *et al.*, *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the

labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group

on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett *et al.*, *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the

false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample.

The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO:1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347 and 349. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be

performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE

EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF cDNA SEQUENCES ENCODING LUNG TUMOR POLYPEPTIDES

This example illustrates the isolation of cDNA molecules encoding lung tumor-specific polypeptides from lung tumor cDNA libraries.

A. ISOLATION OF CDNA SEQUENCES FROM A LUNG SQUAMOUS CELL CARCINOMA LIBRARY

A human lung squamous cell carcinoma cDNA expression library was constructed from poly A^+ RNA from a pool of two patient tissues using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD) following the manufacturer's protocol. Specifically, lung carcinoma tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A^+ RNA was then purified using an oligo dT cellulose column as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with BstXI/EcoRI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with cDNA size fractionation columns (BRL Life Technologies), the cDNA was ligated into the BstXI/NotI site of pcDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human lung cDNA expression library was prepared from a pool of four tissue specimens. The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The lung squamous cell carcinoma library contained 2.7×10^6 independent colonies, with 100% of clones having an insert and

the average insert size being 2100 base pairs. The normal lung cDNA library contained 1.4 x 10^6 independent colonies, with 90% of clones having inserts and the average insert size being 1800 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA

cDNA library subtraction was performed using the above lung squamous cell carcinoma and normal lung cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a lung squamous cell carcinoma-specific subtracted cDNA library was generated as follows. Normal tissue cDNA library (80 μg) was digested with BamHI and XhoI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 133 μl of H_2O, heat-denatured and mixed with 133 μl (133 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (67 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H_2O to form the driver DNA.

To form the tracer DNA, 10 μg lung squamous cell carcinoma cDNA library was digested with NotI and SpeI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech, Palo Alto, CA). Typically, 5 μg of cDNA was recovered after the sizing column. Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H_2O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 ^{0}C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H_2O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 ^{0}C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted

cDNA was ligated into NotI/SpeI site of chloramphenicol resistant pBCSK$^+$ (Stratagene, La Jolla, CA) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a lung squamous cell carcinoma specific subtracted cDNA library (herein after referred to as "lung subtraction I").

A second lung squamous cell carcinoma specific subtracted cDNA library (referred to as "lung subtraction II") was generated in a similar way to the lung subtraction library I, except that eight frequently recovered genes from lung subtraction I were included in the driver DNA, and 24,000 independent clones were recovered.

To analyze the subtracted cDNA libraries, plasmid DNA was prepared from 320 independent clones, randomly picked from the subtracted lung squamous cell carcinoma specific libraries. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A and/or Model 377 (Foster City, CA). The cDNA sequences for sixty isolated clones are provided in SEQ ID NO: 1-60. These sequences were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). No significant homologies were found to the sequences provided in SEQ ID NO: 2, 3, 19, 38 and 46. The sequences of SEQ ID NO: 1, 6-8, 10-13, 15, 17, 18, 20-27, 29, 30, 32, 34-37, 39-45, 47-49, 51, 52, 54, 55 and 57-59 were found to show some homology to previously identified expressed sequence tags (ESTs). The sequences of SEQ ID NO: 9, 28, 31 and 33 were found to show some homology to previously identified non-human gene sequences and the sequences of SEQ ID NO: 4, 5, 14, 50, 53, 56 and 60 were found to show some homology to gene sequences previously identified in humans.

The subtraction procedure described above was repeated using the above lung squamous cell carcinoma cDNA library as the tracer DNA, and the above normal lung tissue cDNA library and a cDNA library from normal liver and heart (constructed from a pool of one sample of each tissue as described above), plus twenty other cDNA clones that were frequently recovered in lung subtractions I and II, as the driver DNA (lung subtraction III). The normal liver and heart cDNA library contained 1.76×10^6 independent colonies, with 100% of clones having inserts and the average insert size being 1600 base

pairs. Ten additional clones were isolated (SEQ ID NO: 61-70). Comparison of these cDNA sequences with those in the gene bank as described above, revealed no significant homologies to the sequences provided in SEQ ID NO: 62 and 67. The sequences of SEQ ID NO: 61, 63-66, 68 and 69 were found to show some homology to previously isolated ESTs and the sequence provided in SEQ ID NO: 70 was found to show some homology to a previously identified rat gene.

In further studies, the subtraction procedure described above was repeated using the above lung squamous cell carcinoma cDNA library as the tracer DNA, and a cDNA library from a pool of normal lung, kidney, colon, pancreas, brain, resting PBMC, heart, skin and esophagus as the driver DNA, with esophagus cDNAs making up one third of the driver material. Since esophagus is enriched in normal epithelial cells, including differentiated squamous cells, this procedure is likely to enrich genes that are tumor specific rather than tissues specific. The cDNA sequences of 48 clones determined in this subtraction are provided in SEQ ID NO: 177-224. The sequences of SEQ ID NO: 177, 178, 180, 181, 183, 187, 192, 195-197, 208, 211, 212, 215, 216, 218 and 219 showed some homology to previously identified genes. The sequences of SEQ ID NO: 179, 182, 184-186, 188-191, 193, 194, 198-207, 209 210, 213, 214, 217, 220 and 224 showed some homology to previously determined ESTs. The sequence of SEQ ID NO: 221-223 showed no homology to any previously determined sequence.

B. ISOLATION OF cDNA SEQUENCES FROM A LUNG ADENOCARCINOMA LIBRARY

A human lung adenocarcinoma cDNA expression library was constructed as described above. The library contained 3.2 x 10^6 independent colonies, with 100% of clones having an insert and the average insert size being 1500 base pairs. Library subtraction was performed as described above using the normal lung and normal liver and heart cDNA expression libraries described above as the driver DNA. Twenty-six hundred independent clones were recovered.

Initial cDNA sequence analysis from 100 independent clones revealed many ribosomal protein genes. The cDNA sequences for fifteen clones isolated in this subtraction are provided in SEQ ID NO: 71-86. Comparison of these sequences with those in the gene bank as described above revealed no significant homologies to the sequence provided in SEQ ID NO: 84. The sequences of SEQ ID NO: 71, 73, 74, 77, 78 and 80-82 were found to show some homology to previously isolated ESTs, and the sequences of SEQ ID NO: 72, 75, 76, 79, 83 and 85 were found to show some homology to previously identified human genes.

In further studies, a cDNA library (referred to as mets3616A) was constructed from a metastatic lung adenocarcinoma. The determined cDNA sequences of 25 clones sequenced at random from this library are provided in SEQ ID NO: 255-279. The mets3616A cDNA library was subtracted against a cDNA library prepared from a pool of normal lung, liver, pancreas, skin, kidney, brain and resting PBMC. To increase the specificity of the subtraction, the driver was spiked with genes that were determined to be most abundant in the mets3616A cDNA library, such as EF1-alpha, integrin-beta and anticoagulant protein PP4, as well as with cDNAs that were previously found to be differentially expressed in subtracted lung adenocarcinoma cDNA libraries. The determined cDNA sequences of 51 clones isolated from the subtracted library (referred to as mets3616A-S1) are provided in SEQ ID NO: 280-330.

Comparison of the sequences of SEQ ID NO: 255-330 with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 255-258, 260, 262-264, 270, 272, 275, 276, 279, 281, 287, 291, 296, 300 and 310. The sequences of SEQ ID NO: 259, 261, 265-269, 271, 273, 274, 277, 278, 282-285, 288-290, 292, 294, 297-299, 301, 303-309, 313, 314, 316, 320-324 and 326-330 showed some homology to previously identified gene sequences, while the sequences of SEQ ID NO: 280, 286, 293, 302, 310, 312, 315, 317-319 and 325 showed some homology to previously isolated expressed sequence tags (ESTs).

EXAMPLE 2

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for seven representative lung tumor polypeptides described in Example 1 were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 ^{0}C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous cell carcinoma from 3 patients, lung adenocarcinoma, colon tumor from 2 patients, breast tumor and prostate tumor), and thirteen different normal tissues (lung from 4 donors, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, stomach, myocardium, retina and testes). Using a 10-fold amount of cDNA, the antigen LST-S1-90 (SEQ ID NO: 3) was found to be expressed at high levels in lung squamous cell carcinoma and in breast tumor, and at low to undetectable levels in the other tissues examined.

The antigen LST-S2-68 (SEQ ID NO: 15) appears to be specific to lung and breast tumor, however, expression was also detected in normal kidney. Antigens LST-S1-169 (SEQ ID NO: 6) and LST-S1-133 (SEQ ID NO: 5) appear to be very abundant in lung tissues (both normal and tumor), with the expression of these two genes being decreased in most of the normal tissues tested. Both LST-S1-169 and LST-S1-133 were also expressed

in breast and colon tumors. Antigens LST-S1-6 (SEQ ID NO: 7) and LST-S2-I2-5F (SEQ ID NO: 47) did not show tumor or tissue specific expression, with the expression of LST-S1-28 being rare and only detectable in a few tissues. The antigen LST-S3-7 (SEQ ID NO: 63) showed lung and breast tumor specific expression, with its message only being detected in normal testes when the PCR was performed for 30 cycles. Lower level expression was detected in some normal tissues when the cycle number was increased to 35. Antigen LST-S3-13 (SEQ ID NO: 66) was found to be expressed in 3 out of 4 lung tumors, one breast tumor and both colon tumor samples. Its expression in normal tissues was lower compared to tumors, and was only detected in 1 out of 4 normal lung tissues and in normal tissues from kidney, ovary and retina. Expression of antigens LST-S3-4 (SEQ ID NO: 62) and LST-S3-14 (SEQ ID NO: 67) was rare and did not show any tissue or tumor specificity. Consistent with Northern blot analyses, the RT-PCT results on antigen LAT-S1-A-10A (SEQ ID NO: 78) suggested that its expression is high in lung, colon, stomach and small intestine tissues, including lung and colon tumors, whereas its expression was low or undetectable in other tissues.

A total of 2002 cDNA fragments isolated in lung subtractions I, II and III, described above, were colony PCR amplified and their mRNA expression levels in lung tumor, normal lung, and various other normal and tumor tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Seventeen non-redundant cDNA clones showed over-expression in lung squamous tumors, with expression in normal tissues tested (lung, skin, lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland) being either undetectable, or 10-fold less compared to lung squamous tumors. The determined partial cDNA sequences for the clone L513S are provided in SEQ ID NO: 87 and 88; those for

L514S are provided in SEQ ID NO: 89 and 90; those for L516S in SEQ ID NO: 91 and 92; that for L517S in SEQ ID NO: 93; that for L519S in SEQ ID NO: 94; those for L520S in SEQ ID NO: 95 and 96; those for L521S in SEQ ID NO: 97 and 98; that for L522S in SEQ ID NO: 99; that for L523S in SEQ ID NO: 100; that for L524S in SEQ ID NO: 101; that for L525S in SEQ ID NO: 102; that for L526S in SEQ ID NO: 103; that for L527S in SEQ ID NO: 104; that for L528S in SEQ ID NO: 105; that for L529S in SEQ ID NO: 106; and those for L530S in SEQ ID NO: 107 and 108. Additionally, the full-length cDNA sequence for L530S is provided in SEQ ID NO: 151, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 152. L530S shows homology to a splice variant of a p53 tumor suppressor homologue, p63. The cDNA sequences of 7 known isoforms of p63 are provided in SEQ ID NO: 331-337, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 338-344, respectively.

Due to polymorphisms, the clone L531S appears to have two forms. A first determined full-length cDNA sequence for L531S is provided in SEQ ID NO: 109, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 110. A second determined full-length cDNA sequence for L531S is provided in SEQ ID NO: 111, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 112. The sequence of SEQ ID NO: 111 is identical to that of SEQ ID NO: 109, except that it contains a 27 bp insertion. Similarly, L514S also has two alternatively spliced forms; the first variant cDNA is listed as SEQ ID NO: 153, with the corresponding amino acid sequence being provided in SEQ ID NO: 155. The second variant form of L514S full-length cDNA is provided in SEQ ID NO: 154, with its corresponding amino acid sequence being provided in SEQ ID NO: 156.

Full length cloning for L524S (SEQ ID NO: 101) yielded two variants (SEQ ID NO: 163 and 164) with the corresponding predicted amino acid sequences of SEQ ID NO: 165 and 166, respectively. Both variants have been shown to encode parathyroid hormone-related peptide.

Attempts to isolate the full-length cDNA for L519S, resulted in the isolation of the extended cDNA sequence provided in SEQ ID NO: 173, which contains a potential

open reading frame. The predicted amino acid sequence encoded by the sequence of SEQ ID NO: 173 is provided in SEQ ID NO: 174. Additionally, the full-length cDNA sequence for the clone of SEQ ID NO: 100 (known as L523S), a known gene, is provided in SEQ ID NO: 175, with the corresponding predicted amino acid sequence provided in SEQ ID NO: 176. In further studies, a full-length cDNA sequence for L523S was isolated from a L523S-positive tumor cDNA library by PCR amplification using gene specific primers designed from the sequence of SEQ ID NO: 175. The determined cDNA sequence is provided in SEQ ID NO: 347. The amino acid sequence encoded by this sequence is provided in SEQ ID NO: 348. This protein sequence differs from the previously published protein sequence at two amino acid positions, namely at positions 158 and 410.

Comparison of the sequences of L514S and L531S (SEQ ID NO: 87 and 88, 89 and 90, and 109, respectively) with those in the gene bank, as described above, revealed no significant homologies to known sequences. The sequences of L513S, L516S, L517S, L519S, L520S and L530S (SEQ ID NO: 87 and 88, 91 and 92, 93, 94, 95 and 96, 107 and 108, respectively) were found to show some homology to previously identified ESTs. The sequences of L521S, L522S, L523S, L524S, L525S, L526S, L527S, L528S and L529S (SEQ ID NO: 97 and 98, 99, 99, 101, 102, 103, 104, 105, and 106, respectively) were found to represent known genes. The determined full-length cDNA sequences for L520S is provided in SEQ ID NO: 113, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 114. Subsequent microarray analysis has shown L520S to be overexpressed in breast tumors in addition to lung squamous tumors.

Further analysis has demonstrated that L529S (SEQ ID NO: 106 and 115), L525S (SEQ ID NO: 102 and 120) and L527S (SEQ ID NO: 104) are cytoskeletal components and potentially squamous cell specific proteins. L529S is connexin 26, a gap junction protein. It is highly expressed in lung squamous tumor 9688T, and moderately over-expressed in two others. However, lower level expression of connexin 26 is also detectable in normal skin, colon, liver and stomach. The over-expression of connexin 26 in some breast tumors has been reported and a mutated form of L529S may result in over-expression in lung tumors. L525S is plakophilin 1, a desmosomal protein found in plaque-

bearing adhering junctions of the skin. Expression levels for L525S mRNA is highly elevated in three out of four lung squamous tumors tested, and in normal skin. L527S has been identified as keratin 6 isoform, type II 58 Kd keratin, and cytokeratin 13 and shows over-expression in squamous tumors and low expression in normal skin, breast and colon tissues. Notably, keratin and keratin-related genes have been extensively documented as potential markers for lung cancer including CYFRA2.1 (Pastor, A., et al, *Eur. Respir. J.*, 10:603-609, 1997). L513S (SEQ ID NO: 87 and 88) shows moderate over-expression in several tumor tissues tested, and encodes a protein that was first isolated as a pemphigus vulgaris antigen.

L520S (SEQ ID NO: 95 and 96) and L521S (SEQ ID NO: 97 and 98) are highly expressed in lung squamous tumors, and L520S is up-regulated in normal salivary gland and L521S is over-expressed in normal skin. Both belong to a family of small proline rich proteins and represent markers for fully differentiated squamous cells. L521S has been described as a specific marker for lung squamous tumor (Hu, R., et al, *Lung Cancer*, 20:25-30, 1998). L515S (SEQ ID NO: 162) encodes IGF-β2 and L516S is an aldose reductase homologue and both are moderately expressed in lung squamous tumors and in normal colon. Notably, L516S (SEQ ID NO: 91 and 92) is up-regulated in metastatic tumors but not primary lung adenocarcinoma, an indication of its potential role in metatasis and a potential prognostic marker. L522S (SEQ ID NO: 99) is moderately over-expressed in lung squamous tumors with minimum expression in normal tissues. L522S has been shown to belong to a class IV alcohol dehydrogenase, ADH7, and its expression profile suggests it is a squamous cell specific antigen. L523S (SEQ ID NO: 100) is moderately over-expressed in lung squamous tumor, human pancreatic cancer cell lines and pancreatic cancer tissues, suggesting this gene may be a shared antigen between pancreatic and lung squamous cell cancer.

L524S (SEQ ID NO: 101) is over-expressed in the majority of squamous tumors tested and is homologous with parathyroid hormone-related peptide (PTHrP), which is best known to cause humoral hypercalcaemia associated with malignant tumors such as leukemia, prostate and breast cancer. It is also believed that PTHrP is most

commonly associated with squamous carcinoma of lung and rarely with lung adenocarcinoma (Davidson, L.A., et al, *J. Pathol.*, 178: 398-401, 1996). L528S (SEQ ID NO: 105) is highly over-expressed in two lung squamous tumors with moderate expression in two other squamous tumors, one lung adenocarcinoma and some normal tissues, including skin, lymph nodes, heart, stomach and lung. It encodes the NMB gene that is similar to the precursor of melanocyte specific gene Pmel17, which is reported to be preferentially expressed in low-metastatic potential melanoma cell lines. This suggests that L528S may be a shared antigen in both melanoma and lung squamous cell carcinoma. L526S (SEQ ID NO: 103) is overexpressed in all lung squamous cell tumor tissues tested and has been shown to share homology with a gene (ATM) in which a mutation causes ataxia telangiectasia, a genetic disorder in humans causing a predisposition to cancer, among other symptoms. ATM encodes a protein that activates p53 mediated cell-cycle checkpoint through direct binding and phosphorylation of the p53 molecule. Approximately 40% of lung cancer is associated with p53 mutations, and it is speculated that over-expression of ATM is a result of compensation for loss of p53 function, but it is unknown whether over-expression is the cause of result of lung squamous cell carcinoma. Additionally, expression of L526S (ATM) is also detected in a metastatic but not lung adenocarcinoma, suggesting a role in metastasis.

Expression of L523S (SEQ ID NO: 175), was also examined by real time RT-PCR as described above. In a first study using a panel of lung squamous tumors, L523S was found to be expressed in 4/7 lung squamous tumors, 2/3 head and neck squamous tumors and 2/2 lung adenocarcinomas, with low level expression being observed in skeletal muscle, soft palate and tonsil. In a second study using a lung adenocarcinoma panel, expression of L523S was observed in 4/9 primary adenocarcinomas, 2/2 lung pleural effusions, 1/1 metastatic lung adenocarcinomas and 2/2 lung squamous tumors, with little expression being observed in normal tissues.

Expression of L523S in lung tumors and various normal tissues was also examined by Northern blot analysis, using standard techniques. In a first study, L523S was found to be expressed in a number of lung adenocarcinomas and squamous cell

carcinomas, as well as normal tonsil. No expression was observed in normal lung. In a second study using a normal tissue blot (HB-12) from Clontech, no expression was observed in brain, skeletal muscle, colon, thymus, spleen, kidney, liver, small intestine, lung or PBMC, although there was strong expression in placenta.

EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF LUNG TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

Eight hundred and fifty seven clones from a cDNA subtraction library, containing cDNA from a pool of two human lung squamous tumors subtracted against eight normal human tissue cDNAs including lung, PBMC, brain, heart, kidney, liver, pancreas, and skin, (Clontech, Palo Alto, CA) were derived and submitted to a first round of PCR amplification. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector P7- Adv vector (Clontech, Palo Alto, CA) and transformed into DH5α *E. coli* (Gibco, BRL). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

One hundred and sixty two positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the EMBL and GenBank databases, as described above, revealed no significant homologies to 13 of these clones, hereinafter referred to as Contigs 13, 16, 17, 19, 22, 24, 29, 47, 49, 56-59. The determined cDNA sequences for these clones are provided in SEQ ID NO: 125, 127-129, 131-133, 142, 144, 148-150, and 157, respectively. Contigs 1, 3-5, 7-10, 12, 11, 15, 20, 31, 33, 38, 39, 41, 43, 44, 45, 48, 50, 53, 54 (SEQ ID NO: 115-124, 126, 130, 134-141, 143, 145-147, respectively) were found to show some degree of homology to previously identified DNA sequences. Contig 57 (SEQ ID NO: 149) was found to represent the clone L519S (SEQ ID NO: 94) disclosed in US. Patent Application No. 09/123,912, filed July 27, 1998. To the best of the inventors' knowledge, none of these sequences have been previously shown to be differentially over-expressed in lung tumors.

mRNA expression levels for representative clones in lung tumor tissues, normal lung tissues (n=4), resting PBMC, salivary gland, heart, stomach, lymph nodes, skeletal muscle, soft palate, small intestine, large intestine, bronchial, bladder, tonsil, kidney, esophagus, bone marrow, colon, adrenal gland, pancreas, and skin, (all derived from human) were determined by RT-PCR as described above. Expression levels using microarray technology, as described above, were examined in one sample of each tissue type unless otherwise indicated.

Contig 3 (SEQ ID NO: 116) was found to be highly expressed in all head and neck squamous cell tumors tested (17/17), and expressed in the majority (8/12) of lung squamous tumors, (high expression in 7/12, moderate in 2/12, and low in 2/12), while showing negative expression for 2/4 normal lung tissues and low expression in the remaining two samples. Contig 3 showed moderate expression in skin and soft palate, and lowered expression levels in resting PBMC, large intestine, salivary gland, tonsil, pancreas, esophagus, and colon. Contig 11 (SEQ ID NO: 124) was found to be expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 14/17, and moderately expressed in 3/17. Additionally, expression in lung squamous tumors showed high expression in 3/12 and moderate in 4/12. Contig 11 was negative for 3/4 normal lung samples, with the remaining sample having only low expression. Contig 11 showed low to moderate reactivity to salivary gland, soft palate, bladder, tonsil, skin, esophagus, and large intestine. Contig 13 (SEQ ID NO: 125) was found to be expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 12/17, and moderately expressed in 5/17. Contig 13 was expressed in 7/12 lung squamous tumors, with high expression in 4/12 and moderate expression in three samples. Analysis of normal lung samples showed negative expression for 2/4 and low to moderate expression in the remaining two samples. Contig 13 did show low to moderate reactivity to resting PBMC, salivary gland, bladder, pancreas, tonsil, skin, esophagus, and large intestine, as well as high expression in soft palate. Subsequent full-length cloning efforts revealed that contig 13 (also known as L761P) maps to the 3' untranslated region of the hSec10p gene. The full-length sequence for this gene is set forth in SEQ ID NO: 368, and encodes the protein set forth in SEQ ID

NO: 369. Contig 16 (SEQ ID NO: 127) was found to be moderately expressed in some head and neck squamous cell tumors (6/17) and one lung squamous tumor; while showing no expression in any normal lung samples tested. Contig 16 did show low reactivity to resting PBMC, large intestine, skin, salivary gland, and soft palate. Contig 17 (SEQ ID NO: 128) was shown to be expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 5/17, and moderately expressed in 12/17. Expression levels in lung squamous tumors showed one tumor sample with high expression and 3/12 with moderate levels. Contig 17 was negative for 2/4 normal lung samples, with the remaining samples having only low expression. Additionally, low level expression was found in esophagus and soft palate. Contig 19 (SEQ ID NO: 129) was found to be expressed in most head and neck squamous cell tumors tested (11/17); with two samples having high levels, 6/17 showing moderate expression, and low expression being found in 3/17. Testing in lung squamous tumors revealed only moderate expression in 3/12 samples. Expression levels in 2/4 of normal lung samples were negative, the two other samples having only low expression. Contig 19 showed low expression levels in esophagus, resting PBMC, salivary gland, bladder, soft palate and pancreas.

Contig 22 (SEQ ID NO: 131), was shown to be expressed in most head and neck squamous cell tumors tested (13/17) with high expression in four of these samples, moderate expression in 6/17, and low expression in 3/17. Expression levels in lung squamous tumors were found to be moderate to high for 3/12 tissues tested, with negative expression in two normal lung samples and low expression in two other samples (n=4). Contig 22 showed low expression in skin, salivary gland and soft palate. Similarly, Contig 24 (SEQ ID NO: 132) was found to be expressed in most head and neck squamous cell tumors tested (13/17) with high expression in three of these samples, moderate expression in 6/17, and low expression in 4/17. Expression levels in lung squamous tumors were found to be moderate to high for 3/12 tissues tested, with negative expression for three normal lung samples and low expression in one sample (n=4). Contig 24 showed low expression in skin, salivary gland and soft palate. Contig 29 (SEQ ID NO: 133) was expressed in nearly all head and neck squamous cell tumors tested (16/17): highly

expressed in 4/17, moderately expressed in 11/17, with low expression in one sample. Also, it was moderately expressed in 3/12 lung squamous tumors, while being negative for 2/4 normal lung samples. Contig 29 showed low to moderate expression in large intestine, skin, salivary gland, pancreas, tonsil, heart and soft palate. Contig 47 (SEQ ID NO: 142) was expressed in most head and neck squamous cell tumors tested (12/17): moderate expression in 10/17, and low expression in two samples. In lung squamous tumors, it was highly expressed in one sample and moderately expressed in two others (n=13). Contig 47 was negative for 2/4 normal lung samples, with the remaining two samples having moderate expression. Also, Contig 47 showed moderate expression in large intestine, and pancreas, and low expression in skin, salivary gland, soft palate, stomach, bladder, resting PBMC, and tonsil.

Contig 48 (SEQ ID NO: 143) was expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 8/17 and moderately expressed in 7/17, with low expression in two samples. Expression levels in lung squamous tumors were high to moderate in three samples (n=13). Contig 48 was negative for one out of four normal lung samples, the remaining showing low or moderate expression. Contig 48 showed moderate expression in soft palate, large intestine, pancreas, and bladder, and low expression in esophagus, salivary gland, resting PBMC, and heart. Contig 49 (SEQ ID NO: 144) was expressed at low to moderate levels in 6/17 head and neck squamous cell tumors tested. Expression levels in lung squamous tumors were moderate in three samples (n=13). Contig 49 was negative for 2/4 normal lung samples, the remaining samples showing low expression. Moderate expression levels in skin, salivary gland, large intestine, pancreas, bladder and resting PBMC were shown, as well as low expression in soft palate, lymph nodes, and tonsil. Contig 56 (SEQ ID NO: 148) was expressed in low to moderate levels in 3/17 head and neck squamous cell tumors tested, and in lung squamous tumors, showing low to moderate levels in three out of thirteen samples. Notably, low expression levels were detected in one adenocarcinoma lung tumor sample (n=2). Contig 56 was negative for 3/4 normal lung samples, and showed moderate expression levels in only large intestine, and low expression in salivary gland, soft palate, pancreas, bladder, and resting

PBMC. Contig 58, also known as L769P, (SEQ ID NO: 150) was expressed at moderate levels in 11/17 head and neck squamous cell tumors tested and low expression in one additional sample. Expression in lung squamous tumors showed low to moderate levels in three out of thirteen samples. Contig 58 was negative for 3/4 normal lung samples, with one sample having low expression. Moderate expression levels in skin, large intestine, and resting PBMC were demonstrated, as well as low expression in salivary gland, soft palate, pancreas, and bladder. Contig 59 (SEQ ID NO: 157) was expressed in some head, neck, and lung squamous tumors. Low level expression of Contig 59 was also detected in salivary gland and large intestine.

The full-length cDNA sequence for Contig 22, also referred to as L763P, is provided in SEQ ID NO: 158, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 159. Real-time RT-PCR analysis of L763P revealed that it is highly expressed in 3/4 lung squamous tumors as well as 4/4 head and neck squamous tumors, with low level expression being observed in normal brain, skin, soft pallet and trachea. Subsequent database searches revealed that the sequence of SEQ ID NO: 158 contains a mutation, resulting in a frameshift in the corresponding protein sequence. A second cDNA sequence for L763P is provided in SEQ ID NO: 345, with the corresponding amino acid sequence being provided in SEQ ID NO: 346. The sequences of SEQ ID NO: 159 and 346 are identical with the exception of the C-terminal 33 amino acids of SEQ ID NO: 159.

The full-length cDNA sequence incorporating Contigs 17, 19, and 24, referred to as L762P, is provided in SEQ ID NO: 160, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 161. Further analysis of L762P has determined it to be a type I membrane protein and two additional variants have been sequenced. Variant 1 (SEQ ID NO: 167, with the corresponding amino acid sequence in SEQ ID NO: 169) is an alternatively spliced form of SEQ ID NO: 160 resulting in deletion of 503 nucleotides, as well as deletion of a short segment of the expressed protein. Variant 2 (SEQ ID NO: 168, with the corresponding amino acid sequence in SEQ ID NO: 170) has a two nucleotide deletion at the 3' coding region in comparison to SEQ ID NO: 160,

resulting in a secreted form of the expressed protein. Real-time RT-PCR analysis of L762P revealed that is over-expressed in 3/4 lung squamous tumors and 4/4 head & neck tumors, with low level expression being observed in normal skin, soft pallet and trachea.

An epitope of L762 was identified as having the sequence KPGHWTYTLNNTHHSLQALK, amino acids 571-590 of SEQ ID NO:161.

The full-length cDNA sequence for contig 56 (SEQ ID NO: 148), also referred to as L773P, is provided in SEQ ID NO: 171, with the predicted amino acid sequence in SEQ ID NO: 172. L773P was found to be identical to dihydroxyl dehydrogenase at the 3' portion of the gene, with divergent 5' sequence. As a result, the 69 N-terminal amino acids are unique. The cDNA sequence encoding the 69 N-terminal amino acids is provided in SEQ ID NO: 349, with the N-terminal amino acid sequence being provided in SEQ ID NO: 350. Real-time PCR revealed that L773P is highly expressed in lung squamous tumor and lung adenocarcinoma, with no detectable expression in normal tissues. Subsequent Northern blot analysis of L773P demonstrated that this transcript is differentially over-expressed in squamous tumors and detected at approximately 1.6 Kb in primary lung tumor tissue and approximately 1.3 Kb in primary head and neck tumor tissue.

Subsequent microarray analysis has shown Contig 58, also referred to as L769S (SEQ ID NO: 150), to be overexpressed in breast tumors in addition to lung squamous tumors.

EXAMPLE 4

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture:

trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 5

PREPARATION OF ANTIBODIES AGAINST LUNG CANCER ANTIGENS

Polyclonal antibodies against the lung cancer antigens L514S, L528S, L531S and L523 (SEQ ID NO: 155, 225, 112 and 176 respectively) were prepared as follows.

Rabbits were immunized with recombinant protein expressed in and purified from *E. coli* as described above. For the initial immunization, 400 μg of antigen combined with muramyl dipeptide (MDP) was injected subcutaneously (S.C.). Animals were boosted S.C. 4 weeks later with 200 μg of antigen mixed with incomplete Freund's Adjuvant (IFA). Subsequent boosts of 100 μg of antigen mixed with IFA were injected S.C. as necessary to induce high antibody titer responses. Serum bleeds from immunized rabbits were tested for antigen-specific reactivity using ELISA assays with purified protein. Polyclonal antibodies against L514S, L528S, L531S and L523S were affinity purified from high titer polyclonal sera using purified protein attached to a solid support.

Immunohistochemical analysis using polyclonal antibodies against L514S was performed on a panel of 5 lung tumor samples, 5 normal lung tissue samples and normal colon, kidney, liver, brain and bone marrow. Specifically, tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize L514S immunoreactivity. L514S was found to be highly expressed in lung tumor

tissue with little or no expression being observed in normal lung, brain or bone marrow. Light staining was observed in colon (epithelial crypt cells positive) and kidney (tubules positive). Staining was seen in normal liver but no mRNA has been detected in this tissue making this result suspect.

Using the same procedure, immunohistochemical analysis using polyclonal antibodies against L528S demonstrated staining in lung tumor and normal lung samples, light staining in colon and kidney and no staining in liver and heart.

Immunohistochemical analysis using polyclonal antibodies against L531S demonstrated staining in lung tumor samples, light membrane staining in most normal lung samples, epithelial staining in colon, tubule staining in kidney, ductal epithelial staining in liver and no staining in heart.

Immunohistochemical analysis using polyclonal antibodies against L523S demonstrated staining in all lung cancer samples tested but no staining in normal lung, kidney, liver, colon, bone marrow or cerebellum.

Generation of polyclonal anti-sera against L762P (SEQ ID NO: 169 and 170) was performed as follows. 400 micrograms of lung antigen was combined with 100 micrograms of muramyldipeptide (MDP). Equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed until an emulsion was formed. Rabbits were injected subcutaneously (S.C.). After four weeks the animals were injected S.C. with 200 micrograms of antigen that was mixed with an equal volume of IFA. Every four weeks animals were boosted with 100 micrograms of antigen. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

Characterization of polyclonal antisera was carried out as follows. 96 well plates were coated with antigen by incubing with 50 microliters (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at RT for 2 hrs. Plates were washed 6 times with PBS/0.01% tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at RT for 30 min. Plates were washed as described above before 50 microliters of goat

anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at RT for 30 min. Plates were washed as described above and 100µl of TMB Microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature the colorimetric reaction was stopped with 100µl 1N H2SO4 and read immediately at 450 nm. Antisera showed strong reactivity to antigen L762P.

Immunohistochemical analysis using polyclonal antibodies against L762S demonstrated staining in all lung cancer samples tested, some light staining in the bronchiole epithelium of normal lung, tubule staining in kidney, light epithelial staining in colon and no staining in heart or liver.

EXAMPLE 6

PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

Immunogenic peptides from the lung cancer antigen L762P (SEQ ID NO: 161) for HLA-A2/K^b-restricted CD8+ T cells were identified as follows.

The location of HLA-A2 binding peptides within the lung cancer antigen L762P (SEQ ID NO: 161) was predicted using a computer program which predicts peptides sequences likely to being to HLA-A*0201 by fitting to the known peptide binding motif for HLA-A*0201 (Rupert *et al.* (1993) *Cell 74*:929; Rammensee *et al.* (1995) *Immunogenetics 41*:178-228). A series of 19 synthetic peptides corresponding to a selected subset of the predicted HLA-A*0201 binding peptides was prepared as described above.

Mice expressing the transgene for human HLA A2/K^b (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with the synthetic peptides, as described by Theobald et al., *Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995 with the following modifications. Mice were immunized with 50µg of L726P peptide and 120µg of an I-A^b binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared. Cells were then resuspended at 7 x 10^6 cells/ml in complete media

(RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10^{-5} M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) L762P peptide- (5μg/ml) and 10mg/ml B_2-microglobulin- (3 μg/ml) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). After six days, cells (5 x 10^5/ml) were restimulated with 2.5 x 10^6/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, *Science 258*:815-818, 1992) and 5 x 10^6/ml irradiated (3000 rads) A2/K^b-transgenic spleen feeder cells. Cells were cultured in the presence of 10U/ml IL-2. Cells were restimulated on a weekly basis as described, in preparation for cloning the line.

Peptide-specific cell lines were cloned by limiting dilution analysis with irradiated (20,000 rads) L762P peptide-pulsed EL4 A2Kb tumor cells (1 x 10^4 cells/well) as stimulators and irradiated (3000 rads) A2/K^b-transgenic spleen cells as feeders (5 x 10^5 cells/ well) grown in the presence of 10U/ml IL-2. On day 7, cells were restimulated as before. On day 14, clones that were growing were isolated and maintained in culture.

Cell lines specific for L762P-87 (SEQ ID NO: 226; corresponding to amino acids 87-95 of SEQ ID NO: 161), L762P-145 (SEQ ID NO: 227; corresponding to amino acids 145-153 of SEQ ID NO: 161), L762P-585 (SEQ ID NO: 228; corresponding to amino acids 585-593 of SEQ ID NO: 161), L762P-425 (SEQ ID NO: 229; corresponding to amino acids 425-433 of SEQ ID NO: 161), L762P(10)-424 (SEQ ID NO: 230; corresponding to amino acids 424-433 of SEQ ID NO: 161) and L762P(10)-458 (SEQ ID NO: 231; corresponding to amino acids 458-467 of SEQ ID NO: 161) demonstrated significantly higher reactivity (as measured by percent specific lysis) against L762P peptide-pulsed EL4-A2/K^b tumor target cells than control peptide-pulsed EL4-A2/K^b tumor target cells.

EXAMPLE 7

IDENTIFICATION OF CD4 IMMUNOGENIC T CELL EPITOPES DERIVED FROM THE LUNG CANCER ANTIGEN L762P

CD4 T cell lines specific for the antigen L762P (SEQ ID NO: 161) were generated as follows.

A series of 28 overlapping peptides were synthesized that spanned approximately 50% of the L762P sequence. For priming, peptides were combined into pools of 4-5 peptides, pulsed at 20 micrograms/ml into dendritic cells for 24 hours. The dendritic cells were then washed and mixed with positively selected CD4+ T cells in 96 well U-bottomed plates. Forty cultures were generated for each peptide pool. Cultures were restimulated weekly with fresh dendritic cells loaded with peptide pools. Following a total of 3 stimulation cycles, cells were rested for an additional week and tested for specificity to antigen presenting cells (APC) pulsed with peptide pools using interferon-gamma ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool or an irrelevant peptide were used as APC. T cell lines that appeared to specifically recognize L762P peptide pools both by cytokine release and proliferation were identified for each pool. Emphasis was placed on identifying T cells with proliferative responses. T cell lines that demonstrated either both L762P-specific cytokine secretion and proliferation, or strong proliferation alone were further expanded to be tested for recognition of individual peptides from the pools, as well as for recognition of recombinant L762P. The source of recombinant L762P was *E. coli*, and the material was partially purified and endotoxin positive. These studies employed 10 micrograms of individual peptides, 10 or 2 micrograms of an irrelevant peptide, and 2 or 0.5 micrograms of either L762P protein or an irrelevant, equally impure, *E. coli* generated recombinant protein. Significant interferon-gamma production and CD4 T cell proliferation was induced by a number of L762P-derived peptides in each pool. The amino acid sequences for these peptides are provided in SEQ ID NO: 232-251. These peptides correspond to amino acids 661-680, 676-696, 526-545, 874-893, 811-830, 871-891, 856-875, 826-845,

795-815, 736-755, 706-725, 706-725, 691-710, 601-620, 571-590, 556-575, 616-635, 646-665, 631-650, 541-560 and 586-605, respectively, of SEQ ID NO: 161.

CD4 T cell lines that demonstrated specificity for individual L762P-derived peptides were further expanded by stimulation with the relevant peptide at 10 micrograms/ml. Two weeks post-stimulation, T cell lines were tested using both proliferation and IFN-gamma ELISA assays for recognition of the specific peptide. A number of previously identified T cells continued to demonstrate L762P-peptide specific activity. Each of these lines was further expanded on the relevant peptide and, following two weeks of expansion, tested for specific recognition of the L762P-peptide in titration experiments, as well as for recognition of recombinant *E. coli*-derived L762P protein. For these experiments, autologous adherent monocytes were pulsed with either the relevant L762P-derived peptide, an irrelevant mammaglobin-derived peptide, recombinant *E. coli*-derived L762P (approx. 50% pure), or an irrelevant *E. coli*-derived protein. The majority of T cell lines were found to show low affinity for the relevant peptide, since specific proliferation and IFN-gamma ratios dramatically decreased as L762P peptide was diluted. However, four lines were identified that demonstrated significant activity even at 0.1 micrograms/ml peptide. Each of these lines (referred to as A/D5, D/F5, E/A7 and E/B6) also appeared to specifically proliferate in response to the *E. coli*-derived L762P protein preparation, but not in response to the irrelevant protein preparation. The amino acid sequences of the L762P-derived peptides recognized by these lines are provided in SEQ ID NO: 234, 249, 236 and 245, respectively. No protein specific IFN-gamma was detected for any of the lines. Lines A/D5, E/A7 and E/B6 were cloned on autologous adherent monocytes pulsed with the relevant peptide at 0.1 (A/D5 and E/A7) or 1 (D/F5) microgram/ml. Following growth, clones were tested for specificity for the relevant peptide. Numerous clones specific for the relevant peptide were identified for lines A/D5 and E/A7.

EXAMPLE 8

PROTEIN EXPRESSION OF LUNG TUMOR-SPECIFIC ANTIGENS

a) Expression of L514S in E. coli

The lung tumor antigen L514S (SEQ ID NO: 89) was subcloned into the expression vector pE32b at NcoI and NotI sites, and transformed into *E. coli* using standard techniques. The protein was expressed from residues 3-153 of SEQ ID NO: 89. The expressed amino acid sequence and the corresponding DNA sequence are provided in SEQ ID NO: 252 and 253, respectively.

b) Expression of L762P

Amino acids 32-944 of the lung tumor antigen L762P (SEQ ID NO: 161), with a 6X His Tag, were subcloned into a modified pET28 expression vector, using kanamycin resistance, and transformed into BL21 CodonPlus using standard techniques. Low to moderate levels of expression were observed. The determined DNA sequence of the L762P expression construct is provided in SEQ ID NO: 254.

EXAMPLE 9

IDENTIFICATION OF MHC CLASS II RESTRICTING ALLELE FOR L-762 PEPTIDE-SPECIFIC RESPONSES

A panel of HLA mismatched antigen presenting cells (APC) were used to identify the MHC class II restricting allele for the L762-peptide specific responses of CD4 T cell clones derived from lines that recognized L762 peptide and recombinant protein. Clones from two lines, AD-5 and EA-7, were tested. The AD-5 derived clones were found to be restricted by the HLA-DRB-1101 allele, and an EA-7 derived clone was found to be restricted by the HLA DRB-0701 or DQB1-0202 allele. Identification of the restriction allele allows targeting of vaccine therapies using the defined peptide to individuals that express the relevant class II allele. Knowing the relevant restricting allele will also enable

clinical monitoring for responses to the defined peptide since only individuals that express the relevant allele will be monitored.

CD4 T cell clones derived from line AD-5 and EA-7 were stimulated on autologous APC pulsed with the specific peptide at 10 μg/ml, and tested for recognition of autologous APC (D72) as well as against a panel of APC partially matched with D72 at class II alleles. Table 1 shows the HLA class typing of the APC tested. Adherent monocytes (generated by 2 hour adherence) from D45, D187, D208, and D326 were used as APC in these experiments. Autologous APC (D72) were not included in the experiment. Each of the APC were pulsed with the relevant peptide (5a for AD-5 and 3e for 3A-7) or the irrelevant mammoglobin peptide at 10 μg/ml, and cultures were established for 10,000 T cells and about 20,000 APC/well. As shown in Table 2, specific proliferation and cytokine production could be detected only when partially matched donor cells were used as APC. Based on the MHC typing analysis, these results strongly suggest that the restricting allele for the L762-specific response of the AD-5 derived clones is HLA-DRB-1101 and for the EA-7 derived clone the restricting allele is HLA DRB-0701 or DQB1-0202.

TABLE 1 - HLA TYPING OF APC

DONOR	DR	DR	DQ	DQ
D72	B1-1101	B1-0701	B1-0202	B1-0301
D45	-3	-15	B1-0201	B1-0602
D187	-4	-15	-1	-7
D208	B1-1101	B1-0407	-3	-3
D326	B1-0301	B1-0701	B1-0202	B1-0201

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TABLE 2 - L762 PEPTIDE RESPONSES MAP TO HLA DR ALLELES

	AD-5																				EA-7	
	A11		B10		C10		C11		E6		F1		F9		G8		G9		G10		G12	
Donor	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN	Prol	γ-IFN
D72 DR-0701, -1101, DQ-0202, -7	46		31		34		24		31		40		55		45		43		91		10	
D45 DR-3, -15, DQ-1, -0201	3.2	1.7	5.5	1.2	3.3	1	1.0	1.5	1.1	1.1	1.6	1.1	1.4	1.3	0.2	1.1	1.1	1.1	1.2	1.5	0.8	1.1
D187 DR-4, -15, DQ-1, -7	1.4	1.2	1.3	1	1.4	1.1	1.4	1.7	1.0	1.1	1.4	1.2	1.2	1.1	0.9	1	1.0	1	1.0	1.6	0.5	1
D208 DR-4, -1101, DQ-3	138	13	38	5.4	18.8	10	14.6	4.6	15.3	6.1	45.9	8.6	73.3	14.1	38.0	7.7	174.3	16.1	113.6	19.6	0.8	1
D326 DR-3, -0701, DQ-0202	0.7	4	0.3	1	0.3	1.4	1.0	2	0.8	1.1	0.3	1.1	0.7	1.1	0.6	1.2	0.4	1	1.2	5	14.1	6.8

EXAMPLE 10

FUSION PROTEINS OF N-TERMINAL AND C-TERMINAL PORTIONS OF L763P

In another embodiment, a Mycobacterium tuberculosis-derived Ra12 polynucleotide is linked to at least an immunogenic portion of a polynucleotide of this invention. Ra12 compositions and methods for their use in enhancing expression of heterologous polynucleotide sequences are described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). Surprisingly, it was discovered that a 14 KD C-terminal fragment of the MTB32A coding sequence expresses at high levels on its own and remains as a soluble protein throughout the purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous antigenic polypeptides with which it is fused. This 14 KD C-terminal fragment of the MTB32A is referred herein as Ra12 and represents a fragment comprising some or all of amino acid residues 192 to 323 of MTB32A.

Recombinant nucleic acids, which encode a fusion polypeptide comprising a Ra12 polypeptide and a heterologous lung tumor polypeptide of interest, can be readily constructed by conventional genetic engineering techniques. Recombinant nucleic acids are constructed so that, preferably, a Ra12 polynucleotide sequence is located 5' to a selected heterologous lung tumor polynucleotide sequence. It may also be appropriate to place a Ra12 polynucleotide sequence 3' to a selected heterologous polynucleotide sequence or to insert a heterologous polynucleotide sequence into a site within a Ra12 polynucleotide sequence.

In addition, any suitable polynucleotide that encodes a Ral2 or a portion or other variant thereof can be used in constructing recombinant fusion polynucleotides comprising Ral2 and one or more lung tumor polynucleotides disclosed herein. Preferred Ral2 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ral2 polypeptide.

Ral2 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ral2 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ral2 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ral2 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ral2 polypeptide or a portion thereof.

Two specific embodiments of fusions between Ral2 and antigens of the present invention are described in this example.

A. N-Terminal Portion of L763P

A fusion protein of full-length Ral2 and the N-terminal portion of L763P (amino acid residues1 1-130) was expressed as a single recombinant protein in E. coli. The cDNA for the N-terminal portion was obtained by PCR with a cDNA for the full length L763P and primers L763F3 5' CGGCGAATTCAT-GGATTGGGGGACGCTGC and 1763RV3 5' CGGCCTCGAGTCACCCCTCTA-TCCGAACCTTCTGC. The PCR product with expected size was recovered from agarose gel, digested with restriction enzymes EcoRI and XhoI, and cloned into the corresponding sites in the expression vector pCRX1. The sequence for the fusion of full-length of Ral2 and L763P-N was confirmed by DNA sequencing (SEQ ID NO:351 and 352).

B. C-Terminal Portion of L763P

A fusion protein of full-length Ra12 and the C-terminal portion of L763P (amino acid residues 100-262) was expressed as a single recombinant protein in E. coli. The cDNA of the C-terminal portion of L763P was obtained by PCR with a cDNA for the full length of L763P and primers L763F4 5' CGGCGAATTCCACGAACCACTCGCAAGTTCAG and L763RV4 5' CGGCTCGAG-TTAGCTTGGGCCTGTGATTGC. The PCR product with expected size was recovered from agarose gel, digested with restriction enzymes EcoRI and XhoI, and cloned into the corresponding sites in the expression vector pCRX1. The sequence for the fusion of full-length Ra12 and L763P-C was confirmed by DNA sequencing (SEQ ID NO:353 and 354).

The recombinant proteins described in this example are useful for the preparation of vaccines, for antibody therapeutics, and for diagnosis of lung tumors.

EXAMPLE 11

EXPRESSION IN E. COLI OF L762P HIS TAG FUSION PROTEIN

PCR was performed on L762P coding region with the following primers:

Forward Primer starting at amino acid 32.

PDM-278 5'ggagtacagcttcaagacaatggg 3' (SEQ ID NO:355) Tm 57°C.

Reverse Primer including natural stop codon after amino acid 920, creating EcoRI site

PDM-280 5'ccatgggaattcattataataattttgttcc 3' (SEQ ID NO:356) TM55°C.

The PCR product was then digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into BL21 (DE3) pLys S and BL21 (DE3) CodonPlus RIL expression hosts.

The protein sequence of expressed recombinant L762P is shown in SEQ ID NO:357, and the DNA sequence is shown in SEQ ID NO:358.

EXAMPLE 12

EXPRESSION IN E. COLI OF L773P A, HIS TAG FUSION PROTEIN

The L773P A coding region was PCR amplified using the following primers:

Forward primer for L773P A starting at amino acid 2.

PDM-299 5'tggcagcccctcttcttcaagtggc 3' (SEQ ID NO:359) Tm63°C.

Reverse primer for L773P A creating artificial stop codon after amino acid 70.

PDM-355 5'cgccagaattcatcaaacaaatctgttagcacc 3' (SEQ ID NO:360) Tm62°C.

The PCR product was then digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into BL21 (DE3) pLys S and BL21 (DE3) CodonPlus RIL expression hosts.

The protein sequence of expressed recombinant L773P A is shown in SEQ ID NO:361, and the DNA sequence is shown in SEQ ID NO:362.

EXAMPLE 13

EPITOPES DERIVED FROM CLONE L773P POLYPEPTIDE

A series of peptides from the L773P amino acid sequence were synthesized and used in *in vitro* priming experiments to generate peptide-specific CD4 T cells. These peptides were 20-mers that overlapped by 15 amino acids and corresponded to amino acids 1-69 of the L773P protein. This region has been demonstrated to be tumor-specific. Following three *in vitro* stimulations, CD4 T cell lines were identified that produced IFNγ in response to the stimulating peptide but not the control peptide. Some of these T cell lines demonstrated recognition of recombinant L773P and L773PA (tumor-sprcidic region) proteins.

To perform the experiments, a total of 11 20-mer peptides overlapping by 15 amino acids and derived from the N-terminal tumor-specific region of L773P corresponding to amino acids 1-69 of L773P were generated by standard procedures (Figure 1). Dendritic cells were derived from PBMC of a normal donor using GMCSF and IL-4 by standard protocol. Purified CD4 T cells were generated from the same donor as the dendritic cells by using MACS beads and negative selection of PBMCs. Dendritic cells were pulsed overnight with the individual 20-mer peptides at a concentration of 10 μg/ml. Pulsed dendritic cells were washed and plated at 1 x 10^4/well of a 96-well U-bottom plates, and purified CD4 cells were added at 1 x 10^5 well. Cultures were supplemented with 10 ng/ml IL-6 and 5 ng/ml IL-12 and incubated at 37°C. Cultures were re-stimulated as above on a weekly basis using as APC dendritic cells generated and pulsed as above, supplemented with 5 ng/ml IL-7 and 10 μg/ml IL-2. Following 3 *in vitro* stimulation cycles, lines (each line corresponds to one well) were tested for cytokine production in response to the stimulating peptide vs. an irrelevant peptide.

A small number of individual CD4 T cell lines (9/528) demonstrated cytokine release (IFNγ) in response to the stimulating peptide but not to control peptide (Figure 3). The CD4 T cell lines that demonstrated specific activity were restimulated on the appropriate L773P peptide and reassayed using autologous dendritic cells pulsed with 10 μg/ml of the appropriate L773P peptide, an irrelevant control peptide, recombinant L773P protein (amino acids 2-364, made in *E. coli*), recombinant L773PA (amino acids 2-71, made in *E. coli*), and an appropriate control protein (L3E, made in *E. coli*). Three of the nine lines tested (1-3C, 1-6G, and 4-12B) recognized the appropriate L773P peptide as well as recombinant L773P and L773PA (Figure 2). Four of the lines tested (4-8A, 4-8E, 4-12D, and 4-12E) recognized the appropriate L773P peptide only. Two of the lines tested (5-6F and 9-3B) demonstrated non-specific activity.

The significant conclusion of this study is that the peptide sequences MWQPLFFKWLLSCCPGSSQI (amino acids 1-20, SEQ ID NO:363) and GSSQIAAAASTQPEDDINTQ (amino acids 16-35, SEQ ID NO: 365) may represent naturally processed epitopes of L773P, which are capable of stimulating human class II MHC-restricted CD4 T cell responses.

On the basis of these results, other epitopes within the scope of the invention include epitopes restricted by other class II MHC; molecules. In addition, variants of the peptide can be produced wherein one or more amino acids are altered such that there is no effect on the ability of the peptides to bind to MHC molecules, no effect on their ability to elicit T cell responses, and no effect on the ability of the elicited T cells to recognize recombinant protein.

The identification of these epitopes from L773P provides strong evidence that this antigen could be used as a component of a cancer vaccine for eliciting T cell responses in lung cancer patients for the treatment of their disease. The peptides could also be used for clinical monitoring of L773P vaccine-treated patients. The peptides could be used directly as a vaccine for lung cancer patients with an L773P-expressing lung tumor.

EXAMPLE 14

SURFACE EXPRESSION OF L762P AND ANTIBODY EPITOPES THEREOF

Rabbits were immunized with full-length Histidine-tagged L762 protein generated in E. coli. Sera was isolated from rabbits and screened for specific recognition of L762P in ELISA assays. One polyclonal serum, 2692L was identified that specifically recognized recombinant L762P protein. The 2692L anti-L762P polyclonal antibodies were purified from the serum by affinity purification using L762P affinity columns. Although L762P is expressed in a subset of primary lung tumor samples, expression appears to be lost in established lung tumor cell lines. Therefore, to characterize surface expression of L762P, a retrovirus construct that expresses L762P was used to transduce primary human fibroblasts as well as 3 lung tumor cell lines (522-23, HTB, and 343T). Transduced lines were selected and expanded to examine L762P surface expression by FACS analysis. For this analysis, non-transduced and transduced cells were harvested using cell dissociation medium, and incubated with 10-50 micrograms/ml of either affinity purified anti-L762P or irrelevant anti-P703P sera. Following a 30 minute incubation on ice, cells were washed and incubated with a secondary, FITC conjugated anti rabbit IgG antibody as above. Cells were washed, resuspended in buffer with Propidium Iodide (PI) and examined by FACS using an

Excalibur fluorescence activated cell sorter. For FACS analysis, PI-positive (i.e. dead/permeabilized cells) were excluded. The polyclonal anti-L762P sera specifically recognized and bound to the surface of L762P-transduced cells but not the non-transduced counterparts. These results demonstrate that L762P is localized to the cell surface of both fibroblasts as well as lung tumor cells.

To identify the peptide epitopes recognized by 2692L, an epitope mapping approach was pursued. A series of overlapping 19-21 mers (5 amino acid overlap) was synthesized that spanned C terminal 1/2 of L762P (amino acids 481-894). In an initial experiment peptides were tested in pools. Specific reactivity with the L762P antiserum was observed with pools A, B, C, and E. To identify the specific peptides recognized by the antiserum, flat bottom 96 well microtiter plates were coated with individual peptides at 10 microgam/ml for 2 hours at 37 C. Wells were then aspirated and blocked with phosphate buffered saline containing 5% (w/v) milk for 2 hours at 37 C, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit anti-L762P serum 2692L was added at 200 or 20 ng/well to triplicate wells in PBST and incubated overnight at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti rabbit IgG (H+L)Affinipure F(ab') fragment at 1:2,000 for 60 minutes. Plates were then washed, and incubated in Tetramethyl benzidine substrate. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450/570 nm using an ELISA plate reader.

The resulting data, presented in Table 1 below, demonstrates that the L762P antisera recognized at least 6 distinct peptide epitopes from the 3' half of L762P.

Peptide (starting amino acid of L762P)	pool	ELISA activity (OD 450-570 200 ng polyclonal serum	20 ng polyclonal serum
A (481)	A	1.76	1.0
B (495)	A	0.14	.06
C (511)	E	0.47	0.18
D (526)	E	0.11	0.09
E (541)	A	0.11	0.04
F (556)	A	0.04	0.02
G (571)	A	0.06	0.02
H (586)	B	0.1	0.03
I (601)	B	0.25	0.06
J (616)	B	0.1	0.03
K (631)	E	0.1	0.08
L (646)	B	0.28	0.12
M (661)	B	0.14	0.03
N (676)	C	0.12	0.1
O (691)	C	1.1	0.23
P (706)	C	0.1	0.03
Q (721)	C	0.11	0.05
R (736)	E	0.12	0.04
S (751)	C	0.15	0.06
U (781)	D	0.12	0.06
V (795)	F	0.07	0.05
X (826)	D	0.1	0.03
Y (841)	D	0.17	0.07
Z (856)	D	0.16	0.08
AA (871)	F	0.17	0.05
BB (874)	F	0.14	0.11
No peptide		0.15	0.045

Individual peptides were identified from each of the pools, and additionally a weak reactivity was identified with peptide BB from pool F. The relevant peptide epitopes are summarized in the table below.

Peptide	Nucleotides of L762P	Amino acids of L762P	Sequence	pool	ELISA activity (OD 450-570) 200 ng	20 ng
A	1441-1500	481-500	SRISSGTGDIFQQHIQLEST	A	1.76	1.0
C	1531-1590	511-530	KNTVTVDNTVGNDTMFLVTW	E	0.47	0.18
I	1801-1860	601-620	AVPPATVEAFVERDSLHFPH	B	0.25	0.06
L	1936-1955	646-665	PETGDPVTLRLLDDGAGADV	B	0.28	0.12
O	2071-2130	691-710	VNHSPSISTPAHSIPGSHAMIL	C	1.1	0.23
BB	2620-2679	874-893	LQSAVSNIAQAPLFIPPNSD	F	0.14	0.11
None	-	-	-	-	0.15	0.05

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed:

1. An isolated polypeptide, comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349 under moderately stringent conditions; and

(c) complements of sequences of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349 or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 110, 112, 114, 152, 155, 156, 159, 161, 165, 166, 169, 170, 172, 174, 176, 226-252, 346, 348 and 350.

4. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349 or a complement of any of the foregoing sequences.

5. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349 or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151,

153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349.

7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349 under moderately stringent conditions.

8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

9. An expression vector, comprising a polynucleotide according to any one of claims claim 4-8.

10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302,

308-310, 313, 315-317, 323, 345, 347 and 349 or a complement of any of the foregoing polynucleotide sequences.

12. A fusion protein, comprising at least one polypeptide according to claim 1.

13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.

16. An isolated polynucleotide encoding a fusion protein according to claim 12.

17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 4;

(c) an antibody according to claim 11;

(d) a fusion protein according to claim 12; and

(e) a polynucleotide according to claim 16.

18. A vaccine comprising an immunostimulant and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 4;

(c) an antibody according to claim 11;

(d) a fusion protein according to claim 12; and

(e) a polynucleotide according to claim 16.

19. A vaccine according to claim 18, wherein the immunostimulant is an adjuvant.

20. A vaccine according to any claim 18, wherein the immunostimulant induces a predominantly Type I response.

21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.

22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 18.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);

in combination with an immunostimulant.

26. A vaccine according to claim 25, wherein the immunostimulant is an adjuvant.

27. A vaccine according to claim 25, wherein the immunostimulant induces a predominantly Type I response.

28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii)encoded by a polynucleotide recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368;

and thereby inhibiting the development of a cancer in the patient.

30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.

31. A method according to any one of claims 21, 22 and 29, wherein the cancer is lung cancer.

32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.

34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.

35. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

(b) polynucleotides encoding a polypeptide of (a); and

(c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.

37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.

38. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NO:_1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that expresses a polypeptide of (i);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

39. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that express a polypeptide of (i);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

40. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

41. A method according to claim 40, wherein the binding agent is an antibody.

42. A method according to claim 41, wherein the antibody is a monoclonal antibody.

43. A method according to claim 40, wherein the cancer is lung cancer.

44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

45. A method according to claim 44, wherein the binding agent is an antibody.

46. A method according to claim 45, wherein the antibody is a monoclonal antibody.

47. A method according to claim 44, wherein the cancer is a lung cancer.

48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

51. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-109, 111, 113, 115-151, 153, 154, 157, 158, 160, 162-164, 167, 168, 171, 173, 175, 177-224, 255-337, 345, 347, 349 and 368 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

54. A diagnostic kit, comprising:

(a) one or more antibodies according to claim 11; and

(b) a detection reagent comprising a reporter group.

55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.

56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

57. A kit according to claim 54, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a lung tumor

protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349 or a complement of any of the foregoing polynucleotides.

59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 173, 175, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253, 254-258, 260, 262-264, 270, 272, 275, 276, 279-281, 286, 287, 291, 293, 295, 296, 300, 302, 308-310, 313, 315-317, 323, 345, 347 and 349.

60. A diagnostic kit, comprising:

(a) an oligonucleotide according to claim 59; and

(b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

ABSTRACT OF THE DISCLOSURE

Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

L773P Peptides	
MWQPLFFKWLLSCCPGSSQI	1-20
FFKWLLSCCPGSSQIAAAAS	6-25
LSCCPGSSQIAAAASTQPED	11-30
GSSQIAAAASTQPEDDINTQ	16-35
AAAASTQPEDDINTQRKKSQ	21-40
TQPEDDINTQRKKSQEKMRE	26-45
DINTQRKKSQEKMREVTDSP	31-50
RKKSQEKMREVTDSPGRPRE	36-55
EKMREVTDSPGRPRELTIPQ	41-60
VTDSPGRPRELTIPQTSSHG	46-65
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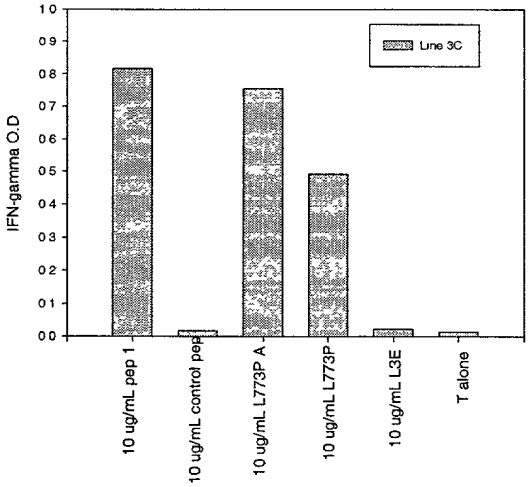
Fig. 1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T alone

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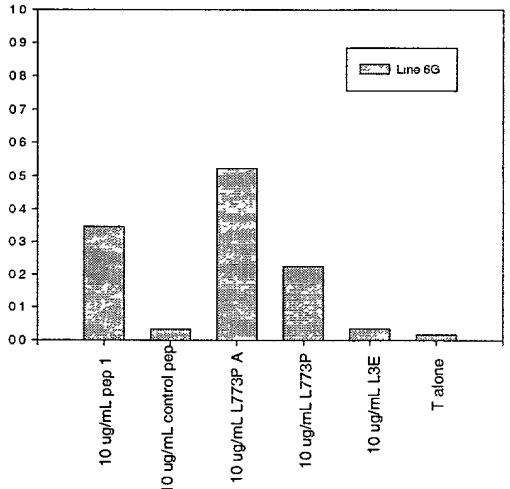
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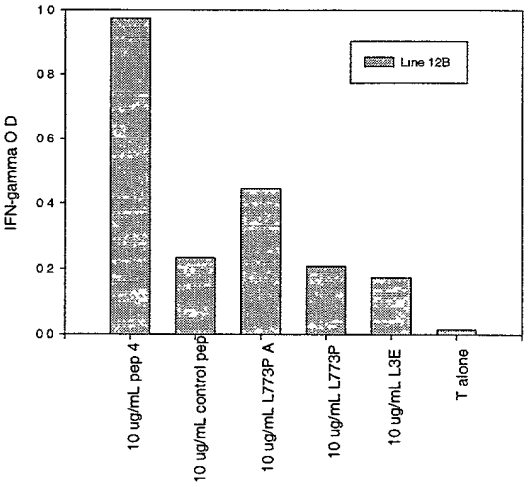
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10 ug/mL L3E
T alone

2C

Fig. 2

D45 L773 CD4 Assay IFN-gamma SI					
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09	16	20	14	08	13
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08	06	08	08	11	20
08	09	13	11	13	07
12	12	09	05	10	**4.2**
14	12	06	06	06	24
Peptide 2					
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24	10	14	08	09	13
07	09	09	14	10	16
08	10	11	12	09	84
06	21	09	15	09	15
10	13	11	16	10	12
09	10	10	10	11	08
21	08	05	08	10	15
Peptide 3					
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15	06	13	07	11	09
08	15	13	06	13	10
07	11	16	09	23	05
10	25	09	24	09	09
Peptide 4					
09	**13.6**	06	08	09	10
09	39	12	09	15	**13.7**
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09	08	07	11	09	**12.3**
08	**2.8**	09	10	12	**4.3**
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11	10	11	10	10	12
09	07	05	07	11	11
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07	15	11	08	11	07
13	10	09	27	14	11
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09	13	19	10	08	12
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13	14	12	14	08	11
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13	10	07	17	06	07
10	17	18	16	10	12
07	08	12	10	15	12
08	16	06	07	15	21
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16	10	08	12	16	12
09	10	11	13	11	09
11	10	14	10	09	09
25	11	09	08	11	10
06	17	11	06	14	11
09	08	12	10	15	10
Peptide 9					
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09	09	*244*	12	13	13
10	11	*263*	12	18	12
06	07	*281*	11	08	10
11	10	*1.3*	07	12	11
07	09	*40.2*	09	13	12
10	08	*440*	08	11	09
09	08	*51*	15	13	16
Peptide 10					
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09	07	08	10	10	13
10	10	06	11	11	15
10	12	11	13	08	11
11	10	11	06	13	13
12	08	10	13	15	10
07	08	12	15	13	12
Peptide 11					
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11	07	14	19	14	16
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Fig. 3

SEQUENCE LISTING

<110> Wang, Tongtong
Fan, Liqun
Kalos, Michael D.
Bangur, Chaitanya S.
Hosken, Nancy
Fanger, Gary R.
Li, Samuel X.
Wang, Aijun
Skeiky, Yasir A.W.
Henderson, Robert A.
McNeill, Patricia D.

<120> COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF LUNG CANCER

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gatgttaagc tttttgaaaa gtttaggtta aacctactgt tgttagatta atgtatttgt 120
tgcttccctt tatctggaat gtggcattag ctttttttatt ttaaccctct ttaattctta 180
ttcaattcca tgacttaagg ttggagagct aaacactggg atttttggat aacagactga 240
cagttttgca taattataat cggcattgta catagaaagg atatggctac cttttgttaa 300
atctgcactt tctaaatatc aaaaaaggga aatgaagtta taaatcaatt tttgtataat 360
ctgtttgaaa catgagtttt atttgcttaa tattagggct ttgccccttt tctgtaagtc 420
tcttgggatc ctgtgtagaa ctgttctcat taaacaccaa acagttaagt ccattctctg 480
gtactagcta caaattcggt ttcatattct acttaacaat ttaaataaac tgaaatattt 540
ctagatggtc tacttctgtt catataaaaa caaaacttga tttccaaaaa aaaaaaaaaa 600
aa 602

<210> 12
<211> 685
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(685)
<223> n = A,T,C or G

<400> 12
actagtcctg tgaaagtaca actgaaggca gaaagtgtta ggattttgca tctaatgttc 60
attatcatgg tattgatgga cctaagaaaa taaaaattag actaagcccc caaataagct 120
gcatgcattt gtaacatgat tagtagattt gaatatatag atgtagtatn ttgggtatct 180
aggtgtttta tcattatgta aaggaattaa agtaaaggac tttgtagttg tttttattaa 240

atatgcatat agtagagtgc aaaaatatag caaaaatana aactaaaggt agaaaagcat 300
tttagatatg ccttaatnta nnaactgtgc caggtggccc tcggaataga tgccaggcag 360
agaccagtgc ctgggtggtg cctccccttg tctgcccccc tgaagaactt ccctcacgtg 420
angtagtgcc ctcgtaggtg tcacgtggan tantggganc aggccgnncn gtnanaagaa 480
ancanngtga nagtttcncc gtngangcng aactgtccct gngccnnnac gctcccanaa 540
cntntccaat ngacaatcga gtttccnnnc tccngnaacc tngccgnnnn cnngcccnnc 600
cantntgnta accccgcgcc cggatcgctc tcnnntcgtt ctcncncnaa ngggntttcn 660
cnnccgccgt cncnnccccg cnncc 685

<210> 13
<211> 694
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(694)
<223> n = A,T,C or G

<400> 13
cactagtcac tcattagcgt tttcaatagg gctcttaagt ccagtagatt acgggtagtc 60
agttgacgaa gatctggttt acaagaacta attaaatgtt tcattgcatt tttgtaagaa 120
cagaataatt ttataaaatg tttgtagttt ataattgccg aaaataattt aaagacactt 180
tttctctgtg tgtgcaaatg tgtgtttgtg atccattttt ttttttttt taggacacct 240
gtttactagc tagctttaca atatgccaaa aaaggatttc tccctgaccc catccgtggt 300
tcaccctctt ttccccccat gctttttgcc ctagtttata acaaaggaat gatgatgatt 360
taaaaagtag ttctgtatct tcagtatctt ggtcttccag aaccctctgg ttgggaaggg 420
gatcattttt tactggtcat ttccctttgg agtgtactac tttaacagat ggaaagaact 480
cattggccat ggaaacagcc gangtgttgg gagccagcag tgcatggcac cgtccggcat 540
ctggcntgat tggtctggct gccgtcattg tcagcacagt gccatgggac atggggaana 600
ctgactgcac ngccaatggt tttcatgaag aatacngcat ncncngtgat cacgtnancc 660
angacgctat gggggncana gggccanttg cttc 694

<210> 14
<211> 679
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(679)
<223> n = A,T,C or G

<400> 14
cagccgcctg catctgtatc cagcgccang tcccgccagt cccagctgcg cgcgcccccc 60
agtcccgnac ccgttcggcc cangctnagt tagncctcac catnccggtc aaaggangca 120
ccaagtgcat caaatacctg cngtncggat ntaaattcat cttctggctt gccgggattg 180
ctgtccntgc cattggacta nggctccgat ncgactctca gaccanganc atcttcganc 240
naganactaa tnatnattnt tccagcttct acacaggagt ctatattctg atcggatccg 300
gcnccctcnt gatgctggtg ggcttcctga gctgctgcgg ggctgtgcaa gagtcccant 360
gcatgctggg actgttcttc ggcttcntct tggtgatatn cgccattgaa atacctgcgg 420
ccatctgggg atattccact ncgatnatgt gattaaggaa ntccacggag ttttacaagg 480
acacgtacaa cnacctgaaa accnnggatg ancccccaccg ggaancnctg aangccatcc 540
actatgcgtt gaactgcaat ggtttggctg gggnccttga acaatttaat cncatacatc 600

tggccccann aaaggacntn ctcgannnct tcnccgtgna attcngttct gatnccatca 660
cagaagtctc gaacaatcc 679

<210> 15
<211> 695
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(695)
<223> n = A,T,C or G

<400> 15
actagtggat aaaggccagg gatgctgctc aacctcctac catgtacagg gacgtctccc 60
cattacaact acccaatccg aagtgtcaac tgtgtcagga ctaanaaacc ctggttttga 120
ttaaaaaagg gcctgaaaaa aggggagcca caaatctgtc tgcttcctca cnttantcnt 180
tggcaaatna gcattctgtc tcnttggctg cngcctcanc ncaaaaaanc ngaactcnat 240
cnggcccagg aatacatctc ncaatnaacn aaattganca aggcnntggg aaatgccnga 300
tgggattatc ntccgcttgt tgancttcta agtttcnttc ccttcattcn accctgccag 360
ccnagttctg ttagaaaaat gccngaattc naacnccggt tttcntactc ngaatttaga 420
tctncanaaa cttcctggcc acnattcnaa ttnanggnca cgnacanatn ccttccatna 480
ancncacccc acntttgana gccangacaa tgactgcntn aantgaaggc ntgaaggaan 540
aactttgaaa ggaaaaaaaa ctttgtttcc ggccccttcc aacncttctg tgttnancac 600
tgccttctng naaccctgga agcccngnga cagtgttaca tgttgttcta nnaaacngac 660
ncttnaatnt cnatcttccc nanaacgatt ncncc 695

<210> 16
<211> 669
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(669)
<223> n = A,T,C or G

<400> 16
cgccgaagca gcagcgcagg ttgtccccgt ttcccctccc ccttcccttc tccggttgcc 60
ttcccgggcc ccttacactc cacagtcccg gtcccgccat gtcccagaaa caagaagaag 120
agaaccctgc ggaggagacc ggcgaggaga agcaggacac gcaggagaaa gaaggtattc 180
tgcctgagag agctgaagag gcaaagctaa aggccaaata cccaagccta ggacaaaagc 240
ctggaggctc cgacttcctc atgaagagac tccagaaagg gcaaaagtac tttgactcng 300
gagactacaa catggccaaa gccaacatga agaataagca gctgccaagt gcangaccag 360
acaagaacct ggtgactggt gatcacatcc ccaccccaca ggatctgccc agagaaagtc 420
ctcgctcgtc accagcaagc ttgcgggtgg ccaagttgaa tgatgctgcc ggggctctgc 480
canatctgag acgcttccct ccctgcccca cccgggtcct gtgctggctc ctgcccttcc 540
tgcttttgca gccangggtc aggaagtggc ncnggtngtg gctggaaagc aaaacccttt 600
cctgttggtg tcccacccat ggagcccctg gggcgagccc angaacttga nccttttttgt 660
tntcttncc 669

<210> 17
<211> 697
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(697)
<223> n = A,T,C or G

<400> 17
gcaagatatg gacaactaag tgagaaggta atnctctact gctctagntn ctccnggcnn 60
gacgcgctga ggagannnac gctggcccan ctgccggcca cacacgggga tcntggtnat 120
gcctgcccan gggancccca ncnctcggan cccatntcac acccgnnccn tncgcccacn 180
ncctggctcn cncngcccng nccagctcnc gnccccctcc gccnnnctcn ttnncntctc 240
cncnccctcc ncnacnacct cctacccncg gctccctccc cagccccccc ccgcaancct 300
ccacnacncc ntcnncncga ancnccnctc gcnctcngcc ccngcccccc gccccccgcc 360
cncnacnncg cgntcccccg cgcncgcngc ctcncccccc cccacnacag ncncacccgc 420
agncacgcnc tccgcccnct gacgccccnn cccgccgcgc tcaccttcat ggnccnacng 480
ccccgctcnc nccnctgcnc gccgncnngg cgccccgccc cnnccgngtn ccncncgnng 540
ccccngcngn angcngtgcg cnncangncc gngccgnncn ncaccctccg nccncccgccc 600
cgcccgctgg gggctcccgc cncgcggntc antccccncc cntncgccca ctntccgntc 660
cnncnctcnc gctcngcgcn cgcccnccnc ccccccc 697

<210> 18
<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 18
ctcgtgtgaa gggtgcagta cctaagccgg agcggggtag aggcgggccg gcacccccctt 60
ctgacctcca gtgccgccgg cctcaagatc agacatggcc cagaacttga acgacttggc 120
gggacggctg cccgccgggc cccggggcat gggcacggcc ctgaagctgt tgctgggggc 180
cggcgccgtg gcctacggtg tgcgcgaatc tgtgttcacc gtggaaggcg ggcncagagc 240
catcttcttc aatcggatcg gtggagtgca caggacacta tcctgggccg anggccttca 300
cttcaggatc cttggttcca gtaccccanc atctatgaca ttcgggccag acctcgaaaa 360
aatctcctcc ctacaggctc caaagaccta cagatggtga atatctccct gcgagtgttg 420
tctcgaccaa tgctcangaa cttcctaaca tgttccancg cctaagggct ggactacnaa 480
gaacgantgt tgccgtccat tgtcacgaag tgctcaagaa tttnggtggc caagttcaat 540
gncctcacnn ctgatcnccc agcggggcca agttanccct ggttgatccc cggggganctg 600
acnnaaaagg gccaaggact tcccctcatc ctggataatg tggccntcac aaagctcaac 660
tttanccacc 670

<210> 19
<211> 606
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(606)
<223> n = A,T,C or G

<400> 19
actagtgcca acctcagctc ccaggccagt tctctgaatg tcgaggagtt ccaggatctc 60
tggcctcagt tgtccttggt tattgatggg ggacaaattg gggatggcca gagccccgag 120
tgtcgccttg gctcaactgt ggttgatttg tctgtgcccg gaaagtttgg catcattcgt 180
ccaggctgtg ccctggaaag tactacagcc atcctccaac agaagtacgg actgctcccc 240
tcacatgcgt cctacctgtg aaactctggg aagcaggaag gcccaagacc tggtgctgga 300
tactatgtgt ctgtccactg acgactgtca aggcctcatt tgcagaggcc accggagcta 360
gggcactagc ctgactttta aggcagtgtg tctttctgag cactgtagac caagcccttg 420
gagctgctgg tttagccttg cacctgggga aaggatgtat ttatttgtat tttcatatat 480
cagccaaaag ctgaatggaa aagttnagaa cattcctagg tggccttatt ctaataagtt 540
tcttctgtct gttttgtttt tcaattgaaa agttattaaa taacagattt agaatctagt 600
gagacc 606

<210> 20
<211> 449
<212> DNA
<213> Homo sapien

<400> 20
actagtaaac aacagcagca gaaacatcag tatcagcagc gtcgccagca ggagaatatg 60
cagcgccaga gccgaggaga acccccgctc cctgaggagg acctgtccaa actcttcaaa 120
ccaccacagc cgcctgccag gatggactcg ctgctcattg caggccagat aaacacttac 180
tgccagaaca tcaaggagtt cactgcccaa aacttaggca agctcttcat ggcccaggct 240
cttcaagaat acaacaacta agaaaaggaa gtttccagaa aagaagttaa catgaactct 300
tgaagtcaca ccagggcaac tcttggaaga aatatatttg catattgaaa agcacagagg 360
atttctttag tgtcattgcc gattttggct ataacagtgt ctttctagcc ataataaaat 420
aaaacaaaat cttgactgct tgctcaaaa 449

<210> 21
<211> 409
<212> DNA
<213> Homo sapien

<400> 21
tatcaatcaa ctggtgaata attaaacaat gtgtggtgtg atcatacaaa gggtaccact 60
caatgataaa aggaacaagc tgcctatatg tggaacaaca tggatgcatt tcagaaactt 120
tatgttgagt gaaagaacaa acacggagaa catactatgt ggttctcttt atgtaacatt 180
acagaaataa aaacagaggc aaccaccttt gaggcagtat ggagtgagat agactggaaa 240
aaggaaggaa ggaaactcta cgctgatgga aatgtctgtg tcttcattgg gtggtagtta 300
tgtggggata tacatttgtc aaaatttatt gaactatata ctaaagaact ctgcatttta 360
ttgggatgta aataatacct caattaaaaa gacaaaaaaa aaaaaaaaa 409

<210> 22
<211> 649
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(649)
<223> n = A,T,C or G

<400> 22

acaattttca ttatcttaag cacattgtac atttctacag aacctgtgat tattctcgca 60
tgataaggat ggtacttgca tatggtgaat tactactgtt gacagtttcc gcagaaatcc 120
tatttcagtg gaccaacatt gtggcatggc agcaaatgcc aacattttgt ggaatagcag 180
caaatctaca agagaccctg gttggttttt cgttttgttt tctttgtttt ttccccttc 240
tcctgaatca gcagggatgg aangagggta gggaagttat gaattactcc ttccagtagt 300
agctctgaag tgtcacattt aatatcagtt ttttttaaac atgattctag ttnaatgtag 360
aagagagaag aaagaggaag tgttcacttt tttaatacac tgatttagaa atttgatgtc 420
ttatatcagt agttctgagg tattgatagc ttgctttatt tctgccttta cgttgacagt 480
gttgaagcag ggtgaataac taggggcata tatatttttt ttttttgtaa gctgtttcat 540
gatgttttct ttggaatttc cggataagtt caggaaaaca tctgcatgtt gttatctagt 600
ctgaagttcn tatccatctc attacaacaa aaacncccag aacggnttg 649

<210> 23
<211> 669
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(669)
<223> n = A,T,C or G

<400> 23
actagtgccg tactggctga aatccctgca ggaccaggaa gagaaccagt tcagactttg 60
tactctcagt caccagctct ggaattagat aaattccttg aagatgtcag gaatgggatc 120
tatcctctga cagcctttgg gctgcctcgg ccccagcagc cacagcagga ggaggtgaca 180
tcacctgtcg tgccccctc tgtcaagact ccgacacctg aaccagctga ggtggagact 240
cgcaaggtgg tgctgatgca gtgcaacatt gagtcggtgg aggagggagt caaacaccac 300
ctgacacttc tgctgaagtt ggaggacaaa ctgaaccggc acctgagctg tgacctgatg 360
ccaaatgaga atatccccga gttggcggct gagctggtgc agctgggctt cattagtgag 420
gctgaccaga gccggttgac ttctctgcta gaagagactt gaacaagttc aattttgcca 480
ggaacagtac cctcaactca gccgctgtca ccgtctcctc ttagagctca ctcgggccag 540
gccctgatct gcgctgtggc tgtcctggac gtgctgcacc ctctgtcctt ccccccagtc 600
agtattacct gtgaagccct tccctccttt attattcagg anggctgggg gggctccttg 660
nttctaacc 669

<210> 24
<211> 442
<212> DNA
<213> Homo sapien

<400> 24
actagtacca tcttgacaga ggatacatgc tcccaaaacg tttgttacca cacttaaaaa 60
tcactgccat cattaagcat cagtttcaaa attatagcca ttcatgattt actttttcca 120
gatgactatc attattctag tcctttgaat ttgtaagggg aaaaaaaaca aaaacaaaaa 180
cttacgatgc actttttctcc agcacatcag atttcaaatt gaaaattaaa gacatgctat 240
ggtaatgcac ttgctagtac tacacacttt ggtacaacaa aaaacagagg caagaaacaa 300
cggaaagaga aaagccttcc tttgttggcc cttaaactga gtcaagatct gaaatgtaga 360
gatgatctct gacgatacct gtatgttctt attgtgtaaa taaaattgct ggtatgaaat 420
gacctaaaaa aaaaaaaaga aa 442

<210> 25
<211> 656
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(656)
<223> n = A,T,C or G

<400> 25
tgcaagtacc acacactgtt tgaattttgc acaaaaagtg actgtaggat caggtgatag 60
ccccggaatg tacagtgtct tggtgcacca agatgccttc taaaggctga cataccttgg 120
accctaatgg ggcagagagt atagccctag cccagtggtg acatgaccac tccctttggg 180
aggcctgagg tagaggggag tggtatgtgt tttctcagtg gaagcagcac atgagtgggt 240
gacaggatgt tagataaagg ctctagttag ggtgtcattg tcatttgaga gactgacaca 300
ctcctagcag ctggtaaagg ggtgctggan gccatggagg anctctagaa acattagcat 360
gggctgatct gattacttcc tggcatcccg ctcactttta tgggaagtct tattagangg 420
atgggacagt tttccatatc cttgctgtgg agctctggaa cactctctaa atttccctct 480
attaaaaatc actgccctaa ctacacttcc tccttgaagg aatagaaatg gaactttctc 540
tgacatantt cttggcatgg ggagccagcc acaaatgana atctgaacgt gtccaggttt 600
ctcctganac tcatctacat agaattggtt aaaccctccc ttggaataag gaaaaa 656

<210> 26
<211> 434
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(434)
<223> n = A,T,C or G

<400> 26
actagttcag actgccacgc caaccccaga aaatacccca catgccagaa aagtgaagtc 60
ctaggtgttt ccatctatgt ttcaatctgt ccatctacca ggcctcgcga taaaaacaaa 120
acaaaaaaac gctgccaggt tttagaagca gttctggtct caaaaccatc aggatcctgc 180
caccagggtt cttttgaaat agtaccacat gtaaaaggga atttggcttt cacttcatct 240
aataactgaa ttgtcaggct ttgattgata attgtagaaa taagtagcct tctgttgtgg 300
gaataagtta taatcagtat tcatctcttt gtttttgtc actcttttct ctctaattgt 360
gtcatttgta ctgtttgaaa aatatttctt ctatnaaatt aaactaacct gccttaaaaa 420
aaaaaaaaaa aaaa 434

<210> 27
<211> 654
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(654)
<223> n = A,T,C or G

<400> 27
actagtccaa cacagtcaga aacattgttt tgaatcctct gtaaaccaag gcattaatct 60
taataaacca ggatccattt aggtaccact tgatataaaa aggatatcca taatgaatat 120
tttatactgc atcctttaca ttagccacta aatacgttat tgcttgatga agacctttca 180

cagaatccta tggattgcag catttcactt ggctacttca tacccatgcc ttaaagaggg 240
gcagtttctc aaaagcagaa acatgccgcc agttctcaag ttttcctcct aactccattt 300
gaatgtaagg gcagctggcc cccaatgtgg ggaggtccga acatttttctg aattcccatt 360
ttcttgttcg cggctaaatg acagtttctg tcattactta gattccgatc tttcccaaag 420
gtgttgattt acaaagaggc cagctaatag cagaaatcat gaccctgaaa gagagatgaa 480
attcaagctg tgagccaggc agganctcag tatggcaaag gtcttgagaa tcngccattt 540
ggtacaaaaa aaatttaaa gcntttatgt tataccatgg aaccatagaa anggcaaggg 600
aattgttaag aanaatttta agtgtccaga cccanaanga aaaaaaaaaa aaaa 654

<210> 28
<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 28
cgtgtgcaca tactgggagg atttccacag ctgcacggtc acagccctta cggattgcca 60
ggaaggggcg aaagatatgt gggataaact gagaaaagaa nccaaaaacc tcaacatcca 120
aggcagctta ttcgaactct gcggcagcgg caacggggcg gcggggtccc tgctcccggc 180
gttcccggtg ctcctggtgt ctctctcggc agctttagcg acctgncttt ccttctgagc 240
gtggggccag ctcccccccgc ggcgcccacc cacnctcact ccatgctccc ggaaatcgag 300
aggaagatca ttagttcttt ggggacgttn gtgattctct gtgatgctga aaaacactca 360
tatagggaat gtgggaaatc ctganctctt tnttatntcg tntgatttct tgtgttttat 420
ttgccaaaat gttaccaatc agtgaccaac cnagcacagc caaaaatcgg acntcngctt 480
tagtccgtct tcacacacag aataagaaaa cggcaaaccc accccacttt tnantttnat 540
tattactaan ttttttctgt tgggcaaaag aatctcagga acngccctgg ggccnccgta 600
ctanagttaa ccnagctagt tncatgaaaa atgatgggct ccncctcaat gggaaagcca 660
agaaaaagnc 670

<210> 29
<211> 551
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(551)
<223> n = A,T,C or G

<400> 29
actagtcctc cacagcctgt gaatcccccct agacctttca agcatagtga gcggagaaga 60
agatctcagc gtttagccac cttacccatg cctgatgatt ctgtagaaaa ggtttcttct 120
ccctctccag ccactgatgg gaaagtattc tccatcagtt ctcaaaatca gcaagaatct 180
tcagtaccag aggtgcctga tgttgcacat ttgccacttg agaagctggg accctgtctc 240
cctcttgact taagtcgtgg ttcagaagtt acagcaccgg tagcctcaga ttcctcttac 300
cgtaatgaat gtcccagggc agaaaaagag gatacncaga tgcttccaaa tccttcttcc 360
aaagcaatag ctgatgggaa gaggagctcc agcagcagca ggaatatcga aaacagaaaa 420
aaaagtgaaa ttgggaagac aaaagctcaa cagcatttgg taaggagaaa aganaagatg 480
aggaaggaag agagaagaga gacnaagatc nctacggacc gnnncggaag aagaagaagn 540
aaaaaanaaa a 551

<210> 30
<211> 684
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(684)
<223> n = A,T,C or G

<400> 30
actagttcta tctggaaaaa gcccgggttg gaagaagctg tggagagtgc gtgtgcaatg 60
cgagactcat ttcttggaag catccctggc aaaaatgcag ctgagtacaa ggttatcact 120
gtgatagaac ctggactgct ttttgagata atagagatgc tgcagtctga agagacttcc 180
agcacctctc agttgaatga attaatgatg gcttctgagt caactttact ggctcaggaa 240
ccacgagaga tgactgcaga tgtaatcgag cttaaaggga aattcctcat caacttagaa 300
ggtggtgata ttcgtgaaga gtcttcctat aaagtaattg tcatgccgac tacgaaagaa 360
aaatgccccc gttgttggaa gtatacagcg ggagtcttca gatacactgt gtcctcgatg 420
tgcagaagtt gtcagtggga aaatagtatt aacagctcac tcgagcaaga accctcctga 480
cagtactggg ctagaagttt ggatggatta tttacaatat aggaaagaaa gccaagaatt 540
aggtnatgag tggatgagta aatggtggan gatggggaat tcaaatcaga attatggaag 600
aagttnttcc tgttactata gaaaggaatt atgtttattt acatgcagaa aatatanatg 660
tgtggtgtgt accgtggatg gaan 684

<210> 31
<211> 654
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(654)
<223> n = A,T,C or G

<400> 31
gcgcagaaaa ggaaccaata tttcagaaac aagcttaata ggaacagctg cctgtacatc 60
aacatcttct cagaatgacc cagaagttat catcgtggga gctggcgtgc ttggctctgc 120
tttggcagct gtgctttcca gagatggaag aaaggtgaca gtcattgaga gagacttaaa 180
agagcctgac agaatagttg gagaattcct gcagccgggt ggttatcatg ttctcaaaga 240
ccttggtctt ggagatacag tggaaggtct tgatgcccag gttgtaaatg gttacatgat 300
tcatgatcag ggaaagcaaa tcagangttc agattcctta ccctctgtca gaaaacaatc 360
aagtgcagag tggaagagct ttccatcacg gaagattcat catgagtctc cggaaagcag 420
ctatggcaga gcccaatgca aagtttattg aaggtgttgt gttacagtta ttagaggaag 480
atgatgttgt gatgggagtt cagtacaagg ataaagagac tgggagatat caaggaactc 540
catgctccac tgactgttgt tgcagatggg cttttctcca anttcaggaa aagcctggtc 600
tcaataaagt ttctgtatca ctcatttggt tggcttctta tgaagaatgc nccc 654

<210> 32
<211> 673
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(673)
<223> n = A,T,C or G

<400> 32
actagtgaag aaaaagaaat tctgatacgg gacaaaaatg ctcttcaaaa catcattctt 60
tatcacctga caccaggagt tttcattgga aaaggatttg aacctggtgt tactaacatt 120
ttaaagacca cacaaggaag caaaatcttt ctgaaagaag taaatgatac acttctggtg 180
aatgaattga aatcaaaaga atctgacatc atgacaacaa atggtgtaat tcatgttgta 240
gataaactcc tctatccagc agacacacct gttggaaatg atcaactgct ggaaatactt 300
aataaattaa tcaaatacat ccaaattaag tttgttcgtg gtagcacctt caaagaaatc 360
cccgtgactg tctatnagcc aattattaaa aaatacacca aaatcattga tgggagtgcc 420
tgtgggaaat aactgaaaaa gagaccgaga agaacgaatc attacaggtc ctgaaataaa 480
atacctagga tttctactgg aggtggagaa acagaagaac tctgaagaaa ttgttacaag 540
aagangtccc aaggtcacca aattcattga aggtggtgat ggtctttatt tgaagatgaa 600
gaaattaaaa gacgcttcag ggagacnccc catgaaggaa ttgccagcca caaaaaaatt 660
cagggattag aaa 673

<210> 33
<211> 673
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(673)
<223> n = A,T,C or G

<400> 33
actagttatt tactttcctc cgcttcagaa ggtttttcag actgagagcc taagcatact 60
ggatctgttg tttcttttgg gtctcacctc atcagtgtgc atagtggcag aaattataaa 120
gaaggttgaa aggagcaggg aaaagatcca gaagcatgtt agttcgacat catcatcttt 180
tcttgaagta tgatgcatat tgcattattt tatttgcaaa ctaggaattg cagtctgagg 240
atcatttaga agggcaagtt caagaggata tgaagatttg agaacttttt aactattcat 300
tgactaaaaa tgaacattaa tgttnaagac ttaagacttt aacctgctgg cagtcccaaa 360
tgaaattatg caactttgat atcatattcc ttgatttaaa ttgggctttt gtgattgant 420
gaaactttat aaagcatatg gtcagttatt tnattaaaaa ggcaaaacct gaaccacctt 480
ctgcacttaa agaagtctaa cagtacaaat acctatctat cttagatgga tntatttntt 540
tntattttta aatattgtac tatttatggt nggtggggct ttcttactaa tacacaaatn 600
aatttatcat ttcaanggca ttctatttgg gtttagaagt tgattccaag nantgcatat 660
ttcgctactg tnt 673

<210> 34
<211> 684
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(684)
<223> n = A,T,C or G

<400> 34
actagtttat tcaagaaaag aacttactga ttcctctgtt cctaaagcaa gagtggcagg 60

tgatcagggc tggtgtagca tccggttcct ttagtgcagc taactgcatt tgtcactgat 120
gaccaaggag gaaatcacta agacatttga gaagcagtgg tatgaacgtt cttggacaag 180
ccacagttct gagccttaac cctgtagttt gcacacaaga acgagctcca cctcccttc 240
ttcaggagga atctgtgcgg atagattggc tggacttttc aatggttctg ggttgcaagt 300
gggcactgtt atggctgggt atggagcgga cagccccagg aatcagagcc tcagcccggc 360
tgcctggttg gaaggtacag gtgttcagca ccttcggaaa aagggcataa agtngtgggg 420
gacaattctc agtccaagaa gaatgcattg accattgctg gctatttgct tncctagtan 480
gaattggatn cattttgac cangatnntt ctnctatgct ttnttgcaat gaaatcaaat 540
cccgcattat ctacaagtgg tatgaagtcc tgcnncccc agagaggctg ttcaggcnat 600
gtcttccaag ggcagggtgg gttacaccat tttacctccc ctctcccccc agattatgna 660
cncagaagga atttntttcc tccc 684

<210> 35
<211> 614
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(614)
<223> n = A,T,C or G

<400> 35
actagtccaa cgcgttngcn aatattcccc tggtagccta cttccttacc cccgaatatt 60
ggtaagatcg agcaatggct tcaggacatg ggttctcttc tcctgtgatc attcaagtgc 120
tcactgcatg aagactggct tgtctcagtg tntcaacctc accagggctg tctcttggtc 180
cacacctcgc tccctgttag tgccgtatga cagcccccat canatgacct tggccaagtc 240
acggtttctc tgtggtcaat gttggtnggc tgattggtgg aaagtanggt ggaccaaagg 300
aagncncgtg agcagncanc nccagttctg caccagcagc gcctccgtcc tactngggtg 360
ttccngtttc tcctggccct gngtgggcta nggcctgatt cgggaanatg cctttgcang 420
gaaggganga taantgggat ctaccaattg attctggcaa aacnatntct aagattnttn 480
tgctttatgt ggganacana tctanctctc atttnntgct gnanatnaca ccctactcgt 540
gntcgancnc gtcttcgatt ttcgganaca cnccantnaa tactggcgtt ctgttgttaa 600
aaaaaaaaaa aaaa 614

<210> 36
<211> 686
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(686)
<223> n = A,T,C or G

<400> 36
gtggctggcc cggttctccg cttctcccca tcccctactt tcctccctcc ctcccttcc 60
ctccctcgtc gactgttgct tgctggtcgc agactccctg acccctccct cacccctccc 120
taacctcggt gccaccggat tgcccttctt ttcctgttgc ccagcccagc cctagtgtca 180
gggcgggggc ctggagcagc ccgaggcact gcagcagaag ananaaaaga cacgacnaac 240
ctcagctcgc cagtccggtc gctngcttcc cgccgcatgg caatnagaca gacgccgctc 300
acctgctctg ggcacacgcg acccgtggtt gatttggcct tcagtggcat caccttatg 360
ggtatttctt aatcagcgct tgcaaagatg gttaacctat gctacgccag ggagatacag 420
gagactggat tggaacattt ttggggtcta aaggtctgtt tggggtgcaa cactgaataa 480

ggatgccacc aaagcagcta cagcagctgc agatttcaca gcccaagtgt gggatgctgt 540
ctcagganat naattgataa cctggctcat aacacattgt caagaatgtg gatttcccca 600
ggatattatt atttgtttac cgggggganag gataactgtt tcncntattt taattgaaca 660
aactnaaaca aaanctaagg aaatcc 686

<210> 37
<211> 681
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(681)
<223> n = A,T,C or G

<400> 37
gagacanacn naacgtcang agaanaaaag angcatggaa cacaanccag gcncgatggc 60
caccttccca ccagcancca gcgccccccа gcngccccca ngnccggang accangactc 120
cancctgnat caatctganc tctattcctg gcccatncct acctcggagg tggangccgn 180
aaaggtcgca cnnncagaga agctgctgcc ancaccancc gccccnnccc tgncgggctn 240
nataggaaac tggtgaccnn gctgcanaat tcatacagga gcacgcgang ggcacnnnct 300
cacactgagt tnnngatgan gcctnaccan ggacctnccc cagcnnattg annacnggac 360
tgcggaggaa ggaagacccc gnacnggatc ctggccggcn tgccaccccc ccacccctag 420
gattatnccc cttgactgag tctctgaggg gctacccgaa cccgcctcca ttccctacca 480
natnntgctc natcgggact gacangctgg ggatnggagg ggctatcccc cancatcccc 540
tnanaccaac agcnacngan natnggggct ccccngggtc ggngcaacnc tcctncaccc 600
cggcgcnggc cttcggtgnt gtcctccntc aacnaattcc naaanggcgg gccccccngt 660
ggactcctcn ttgttccctc c 681

<210> 38
<211> 687
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(687)
<223> n = A,T,C or G

<400> 38
canaaaaaaa aaaacatggc cgaaaccagn aagctgcgcg atggcgccac ggcccctctt 60
ctcccggcct gtgtccggaa ggtttccctc cgaggcgccc cggctcccgc aagcggagga 120
gagggcggga cntgccgggg ccggagctca naggccctgg ggccgctctg ctctcccgcc 180
atcgcaaggg cggcgctaac ctnaggcctc cccgcaaagg tccccnangc ggnggcggcg 240
gggggctgtg anaaccgcaa aaanaacgct gggcgcgcng cgaacccgtc cacccccgcg 300
aagganana ttccacagan gcagcgtttc cacagcccan agccacnttt ctagggtgat 360
gcaccccagt aagttcctgn cggggaagct caccgctgtc aaaaaanctc ttcgctccac 420
cggcgcacna aggggangan ggcangangc tgccgcccgc acaggtcatc tgatcacgtc 480
gcccgcccta ntctgctttt gtgaatctcc actttgttca accccacccg ccgttctctc 540
ctccttgcgc cttcctctna ccttaanaac cagcttcctc tacccnatng tanttnctct 600
gcncnngtng aaattaattc ggtccnccgg aacctcttnc ctgtggcaac tgctnaaaga 660
aactgctgtt ctgnttactg cngtccc 687

<210> 39

<211> 695
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(695)
<223> n = A,T,C or G

<400> 39
actagtctgg cctacaatag tgtgattcat gtaggacttc tttcatcaat tcaaaacccc 60
tagaaaaacg tatacagatt atataagtag ggataagatt tctaacattt ctgggctctc 120
tgacccctgc gctagactgt ggaaagggag tattattata gtatacaaca ctgctgttgc 180
cttattagtt ataacatgat aggtgctgaa ttgtgattca caatttaaaa acactgtaat 240
ccaaactttt ttttttaact gtagatcatg catgtgaatg ttaatgttaa tttgttcaan 300
gttgttatgg gtagaaaaaa ccacatgcct taaaatttta aaaagcaggg cccaaactta 360
ttagtttaaa attaggggta tgtttccagt ttgttattaa ntggttatag ctctgtttag 420
aanaaatcna ngaacangat ttngaaantt aagntgacat tatttnccag tgacttgtta 480
atttgaaatc anacacggca ccttccgttt tggtnctatt ggnntttgaa tccaancngg 540
ntccaaatct tnttggaaac ngtccnttta acttttttac nanatcttat ttttttattt 600
tggaatggcc ctatttaang ttaaaagggg ggggnnccac naccattcnt gaataaaact 660
naatatatat ccttggtccc ccaaaattta aggng 695

<210> 40
<211> 674
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(674)
<223> n = A,T,C or G

<400> 40
actagtagtc agttgggagt ggttgctata ccttgacttc atttatatga atttccactt 60
tattaaataa tagaaaagaa aatcccggtg cttgcagtag agttatagga cattctatgc 120
ttacagaaaa tatagccatg attgaaatca aatagtaaag gctgttctgg ctttttatct 180
tcttagctca tcttaaataa gtagtacact tgggatgcag tgcgtctgaa gtgctaatca 240
gttgtaacaa tagcacaaat cgaacttagg atgtgtttct tctcttctgt gtttcgattt 300
tgatcaattc tttaattttg ggaacctata atacagtttt cctattcttg gagataaaaa 360
ttaaatggat cactgatatt taagtcattc tgcttctcat ctnaatattc catattctgt 420
attagganaa antacctccc agcacagccc cctctcaaac cccacccaaa accaagcatt 480
tggaatgagt ctcctttatt tccgaantgt ggatggtata acccatatcn ctccaatttc 540
tgnttgggtt gggtattaat ttgaactgtg catgaaaagn ggnaatcttt nctttgggtc 600
aaantttncc ggttaatttg nctngncaaa tccaatttnc tttaagggtg tctttataaa 660
atttgctatt cngg 674

<210> 41
<211> 657
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(657)
<223> n = A,T,C or G

<400> 41
gaaacatgca agtaccacac actgtttgaa ttttgcacaa aaagtgactg tagggatcag 60
gtgatagccc cggaatgtac agtgtcttgg tgcaccaaga tgccttctaa aggctgacat 120
accttgggac cctaatgggg cagagagtat agccctagcc cagtggtgac atgaccactc 180
cctttgggag gctgaagtta aagggaatgg tatgtgtttt ctcatggaag cagcacatga 240
atnggtnaca ngatgttaaa ntaaggntct antttgggtg tcttgtcatt tgaaaaantg 300
acacactcct ancanctggt aaaggggtgc tggaagccat ggaagaactc taaaaacatt 360
agcatgggct gatctgatta cttcctggca tcccgctcac ttttatggga agtcttatta 420
naaggatggg anantttcc atatccttgc tgttggaact ctggaacact ctctaaattt 480
ccctctatta aaaatcactg nccttactac acttcctcct tganggaata gaaatggacc 540
tttctctgac ttagttcttg gcatggganc cagcccaaat taaaatctga cttntccggt 600
ttctccngaa ctcacctact tgaattggta aaacctcctt tggaattagn aaaaacc 657

<210> 42
<211> 389
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(389)
<223> n = A,T,C or G

<400> 42
actagtgctg aggaatgtaa acaagtttgc tgggccttgc gagacttcac caggttgttt 60
cgatagctca cactcctgca ctgtgcctgt cacccaggaa tgtcttttt aattagaaga 120
caggaagaaa acaaaaacca gactgtgtcc cacaatcaga aacctccgtt gtggcagang 180
ggccttcacc gccaccaggg tgtcccgcca gacagggaga gactccagcc ttctgaggcc 240
atcctgaaga attcctgttt gggggttgtg aaggaaaatc acccggattt aaaaagatgc 300
tgttgcctgc ccgcgtngtn gggaagggac tggtttcctg gtgaatttct taaaagaaaa 360
atattttaag ttaagaaaaa aaaaaaaaa 389

<210> 43
<211> 279
<212> DNA
<213> Homo sapien

<400> 43
actagtgaca agctcctggt cttgagatgt cttctcgtta aggagatggg ccttttggag 60
gtaaaggata aaatgaatga gttctgtcat gattcactat tctagaactt gcatgacctt 120
tactgtgtta gctctttgaa tgttcttgaa attttagact ttctttgtaa acaaataata 180
tgtccttatc attgtataaa agctgttatg tgcaacagtg tggagatcct tgtctgattt 240
aataaaatac ttaaacactg aaaaaaaaaa aaaaaaaaa 279

<210> 44
<211> 449
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(449)
<223> n = A,T,C or G

<400> 44
actagtagca tcttttctac aacgttaaaa ttgcagaagt agcttatcat taaaaaacaa 60
caacaacaac aataacaata aatcctaagt gtaaatcagt tattctaccc cctaccaagg 120
atatcagcct gttttttccc ttttttctcc tgggaataat tgtgggcttc ttcccaaatt 180
tctacagcct ctttcctctt ctcatgcttg agcttccctg tttgcacgca tgcgttgtgc 240
aagantgggc tgtttngctt ggantncggt ccnagtggaa ncatgctttc ccttgttact 300
gttggaagaa actcaaacct tcnancccta ggtgttncca ttttgtcaag tcatcactgt 360
atttttgtac tggcattaac aaaaaaagaa atnaaatatt gttccattaa actttaataa 420
aactttaaaa gggaaaaaaa aaaaaaaaa 449

<210> 45
<211> 559
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(559)
<223> n = A,T,C or G

<400> 45
actagtgtgg gggaatcacg gacacttaaa gtcaatctgc gaaataattc ttttattaca 60
cactcactga agtttttgag tcccagagag ccattctatg tcaaacattc caagtactct 120
ttgagagccc agcattacat caacatgccc gtgcagttca aaccgaagtc cgcaggcaaa 180
tttgaagctt tgcttgtcat tcaaacagat gaaggcaaga gtattgctat tcgactaatt 240
ggtgaagctc ttggaaaaaa ttnactagaa tacttttttgt gttaagttaa ttacataagt 300
tgtattttgt taactttatc tttctacact acaattatgc ttttgtatat atattttgta 360
tgatggatat ctataattgt agattttgtt tttacaagct aatactgaag actcgactga 420
aatattatgt atctagccca tagtattgta cttaactttt acagggtgaa aaaaaaattc 480
tgtgtttgca ttgattatga tattctgaat aaatatggga atatatttta atgtgggtaa 540
aaaaaaaaaa aaaaaggaa 559

<210> 46
<211> 731
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

<400> 46
actagttcta gtaccatggc tgtcatagat gcaaccatta tattccattt agtttcttcc 60
tcaggttccc taacaattgt ttgaaactga atatatatgt ttatgtatgt gtgtgtgttc 120
actgtcatgt atatggtgta tatgggatgt gtgcagtttt cagttatata tatattcata 180
tatacatatg catatatatg tataatatac atatatacat gcatacactt gtataatata 240
catatatata cacatatatg cacacatatn atcactgagt tccaaagtga gtctttattt 300
ggggcaattg tattctctcc ctctgtctgc tcactgggcc tttgcaagac atagcaattg 360
cttgatttcc tttggataag agtcttatct tcggcactct tgactctagc cttaacttta 420
gatttctatt ccagaatacc tctcatatct atcttaaaac ctaaganggg taaagangtc 480

ataagattgt agtatgaaag antttgctta gttaaattat atctcaggaa actcattcat 540
ctacaaatta aattgtaaaa tgatggtttg ttgtatctga aaaaatgttt agaacaagaa 600
atgtaactgg gtacctgtta tatcaaagaa cctcnattta ttaagtctcc tcatagccan 660
atccttatat ngccctctct gacctgantt aatananact tgaataatga atagttaatt 720
taggnttggg c 731

<210> 47
<211> 640
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(640)
<223> n = A,T,C or G

<400> 47
tgcgngccgg tttggccctt ctttgtanga cactttcatc cgccctgaaa tcttcccgat 60
cgttaataac tcctcaggtc cctgcctgca cagggttttt tcttantttg ttgcctaaca 120
gtacaccaaa tgtgacatcc tttcaccaat atngattnct tcataccaca tcntcnatgg 180
anacgactnc aacaattttt tgatnacccn aaanactggg ggctnnaana agtacantct 240
ggagcagcat ggacctgtcn gcnactaang gaacaanagt nntgaacatt tacacaacct 300
ttggtatgtc ttactgaaag anagaaacat gcttctnncc ctagaccacg aggncaaccg 360
caganattgc caatgccaag tccgagcggt tagatcaggt aatacattcc atggatgcat 420
tacatacntt gtccccgaaa nanaagatgc cctaanggct tcttcanact ggtccngaaa 480
acanctacac ctggtgcttg ganaacanac tctttggaag atcatctggc acaagttccc 540
cccagtgggt tttnccttgg cacctanctt accanatcna ttcggaancc attctttgcc 600
ntggcnttnt nttgggacca ntcttctcac aactgnaccc 640

<210> 48
<211> 257
<212> DNA
<213> Homo sapien

<400> 48
actagtatat gaaaatgtaa atatcacttg tgtactcaaa caaaagttgg tcttaagctt 60
ccaccttgag cagccttgga aacctaacct gcctctttta gcataatcac attttctaaa 120
tgattttctt tgttcctgaa aaagtgattt gtattagttt tacatttgtt ttttggaaga 180
ttatatttgt atatgtatca tcataaaata tttaaataaa aagtatcttt agagtgaaaa 240
aaaaaaaaaa aaaaaaa 257

<210> 49
<211> 652
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(652)
<223> n = A,T,C or G

<400> 49
actagttcag atgagtggct gctgaagggg ccccccttgtc attttcatta taacccaatt 60
tccacttatt tgaactctta agtcataaat gtataatgac ttatgaatta gcacagttaa 120

gttgacacta gaaactgccc atttctgtat tacactatca aataggaaac attggaaaga 180
tggggaaaaa aatcttattt taaaatggct tagaaagttt tcagattact ttgaaaattc 240
taaacttctt tctgtttcca aaacttgaaa atatgtagat ggactcatgc attaagactg 300
ttttcaaagc tttcctcaca tttttaaagt gtgattttcc ttttaatata catatttatt 360
ttctttaaag cagctatatc ccaacccatg actttggaga tatacctatn aaaccaatat 420
aacagcangg ttattgaagc agctttctca aatgttgctt cagatgtgca agttgcaaat 480
tttattgtat ttgtanaata caatttttgt tttaaactgt atttcaatct atttctccaa 540
gatgcttttc atatagagtg aaatatccca ngataactgc ttctgtgtcg tcgcatttga 600
cgcataactg cacaaatgaa cagtgtatac ctcttggttg tgcattnacc cc 652

<210> 50
<211> 650
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(650)
<223> n = A,T,C or G

<400> 50
ttgcgctttg attttttag ggcttgtgcc ctgtttcact tatagggtct agaatgcttg 60
tgttgagtaa aaaggagatg cccaatattc aaagctgcta aatgttctct ttgccataaa 120
gactccgtgt aactgtgtga acacttggga tttttctcct ctgtcccgag gtcgtcgtct 180
gctttctttt ttgggttctt tctagaagat tgagaaatgc atatgacagg ctgagancac 240
ctccccaaac acacaagctc tcagccacan gcagcttctc cacagcccca gcttcgcaca 300
ggctcctgga nggctgcctg ggggaggcag acatgggagt gccaaggtgg ccagatggtt 360
ccaggactac aatgtcttta tttttaactg tttgccactg ctgccctcac ccctgcccgg 420
ctctggagta ccgtctgccc canacaagtg ggantgaaat gggggtgggg gggaacactg 480
attcccantt agggggtgcc taactgaaca gtagggatan aaggtgtgaa cctgngaant 540
gcttttataa attatnttcc ttgttanatt tatttttaa tttaatctct gttnaactgc 600
ccngggaaaa ggggaaaaaa aaaaaaaaat tctntttaaa cacatgaaca 650

<210> 51
<211> 545
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(545)
<223> n = A,T,C or G

<400> 51
tggcgtgcaa ccagggtagc tgaagtttgg gtctgggact ggagattggc cattaggcct 60
cctganattc cagctccctt ccaccaagcc cagtcttgct acgtggcaca gggcaaacct 120
gactcccttt gggcctcagt ttcccctccc cttcatgana tgaaaagaat actacttttt 180
cttgttggtc taacnttgct ggacncaaag tgtngtcatt attgttgtat tgggtgatgt 240
gtncaaaact gcagaagctc actgcctatg agaggaanta agagagatag tggatganag 300
ggacanaagg agtcattatt tggtatagat ccacccntcc caacctttct ctcctcagtc 360
cctgcnnctc atgtntctgg tntggtgagt cctttgtgcc accanccatc atgctttgca 420
ttgctgccat cctgggaagg gggtgnatcg tctcacaact tgttgtcatc gtttganatg 480
catgctttct tnatnaaaca aanaaannaa tgtttgacag ngtttaaaat aaaaaanaaa 540
caaaa 545

<210> 52
<211> 678
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(678)
<223> n = A,T,C or G

<400> 52
actagtagaa gaactttgcc gcttttgtgc ctctcacagg cgcctaaagt cattgccatg 60
ggaggaagac gatttggggg gggaggggggg gggggcangg tccgtggggc tttccctant 120
ntatctccat ntccantgnn cnntgtcgcc tcttccctcg tcncattnga anttantccc 180
tggncccnnn nccctctccn ncctncncct ccccccctccg ncncctccnn ctttttntan 240
ncttccccat ctccntcccc cctnanngtc ccaacnccgn cagcaatnnc ncacttnctc 300
nctccncncc tccnnccgtt cttctnttct cnacntntnc ncnnntnccn tgccnntnaa 360
annctctccc cnctgcaanc gattctctcc ctccncnnan ctntccactc cntncttctc 420
ncncgctcct nttcntcnnc ccacctctcn ccttcgnccc cantacnctc nccncccttn 480
cgnntcnttn nnntcctcnn accncccncc tcccttcncc cctcttctcc ccggtntntc 540
tctctcccnc nncncnncct cnncccntcc nngcgnccnt ttccgccccn cnccnccntt 600
ccttcntcnc cantccatcn cntntnccat nctncctncc nctcacnccc gctncccccn 660
ntctctttca cacngtcc 678

<210> 53
<211> 502
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 53
tgaagatcct ggtgtcgcca tgggccgccg ccccgcccgt tgttaccggt attgtaagaa 60
caagccgtac ccaaagtctc gcttctgccg aggtgtccct gatgccaaaa ttcgcatttt 120
tgacctgggg cggaaaaang caaaantgga tgagtctccg ctttgtggcc acatggtgtc 180
agatcaatat gagcagctgt cctctgaagc cctgnangct gcccgaattt gtgccaataa 240
gtacatggta aaaagtngtg gcnaagatgc ttccatatcc gggtgcggnt ccacccccttc 300
cacgtcatcc gcatcaacaa gatgttgtcc tgtgctgggg ctgacaggct cccaacaggc 360
atgcgaagtg cctttggaaa acccanggca ctgtggccag ggttcacatt gggccaattn 420
atcatgttca tccgcaccaa ctgcagaaca angaacntgt naattnaagc cctgcccagg 480
gncaanttca aatttcccgg cc 502

<210> 54
<211> 494
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(494)

<223> n = A,T,C or G

<400> 54
actagtccaa gaaaaatatg cttaatgtat attacaaagg ctttgtatat gttaacctgt 60
tttaatgcca aaagtttgct ttgtccacaa tttccttaag acctcttcag aaagggattt 120
gtttgcctta atgaatactg ttgggaaaaa acacagtata atgagtgaaa agggcagaag 180
caagaaattt ctacatctta gcgactccaa gaagaatgag tatccacatt tagatggcac 240
attatgagga ctttaatctt tccttaaaca caataatgtt ttctttttc ttttattcac 300
atgatttcta agtatatttt tcatgcagga cagtttttca accttgatgt acagtgactg 360
tgttaaattt ttctttcagt ggcaacctct ataatcttta aaatatggtg agcatcttgt 420
ctgttttgaa ngggatatga cnatnaatct atcagatggg aaatcctgtt tccaagttag 480
aaaaaaaaaa aaaa 494

<210> 55
<211> 606
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(606)
<223> n = A,T,C or G

<400> 55
actagtaaaa agcagcattg ccaaataatc cctaattttc cactaaaaat ataatgaaat 60
gatgttaagc tttttgaaaa gtttaggtta aacctactgt tgttagatta atgtatttgt 120
tgcttccctt tatctggaat gtggcattag ctttttttatt ttaaccctct ttaattctta 180
ttcaattcca tgacttaagg ttggagagct aaacactggg atttttggat aacagactga 240
cagttttgca taattataat cggcattgta catagaaagg atatggctac cttttgttaa 300
atctgcactt tctaaatatc aaaaaaggga aatgaagtat aaatcaattt ttgtataatc 360
tgtttgaaac atganttta tttgcttaat attanggctt tgccctttc tgttagtctc 420
ttgggatcct gtgtaaaact gttctcatta aacaccaaac agttaagtcc attctctggt 480
actagctaca aattccgttt catattctac ntaacaattt aaattaactg aaatatttct 540
anatggtcta cttctgtcnt ataaaaacna aacttgantt nccaaaaaaa aaaaaaaaaa 600
aaaaaa 606

<210> 56
<211> 183
<212> DNA
<213> Homo sapien

<400> 56
actagtatat ttaaacttac aggcttattt gtaatgtaaa ccaccatttt aatgtactgt 60
aattaacatg gttataatac gtacaatcct tccctcatcc catcacacaa ctttttttgt 120
gtgtgataaa ctgattttgg tttgcaataa aaccttgaaa aataaaaaaa aaaaaaaaaa 180
aaa 183

<210> 57
<211> 622
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(622)
<223> n = A,T,C or G

<400> 57
actagtcact actgtcttct ccttgtagct aatcaatcaa tattcttccc ttgcctgtgg 60
gcagtggaga gtgctgctgg gtgtacgctg cacctgccca ctgagttggg gaaagaggat 120
aatcagtgag cactgttctg ctcagagctc ctgatctacc ccacccccta ggatccagga 180
ctgggtcaaa gctgcatgaa accaggccct ggcagcaacc tgggaatggc tggaggtggg 240
agagaacctg acttctcttt ccctctccct cctccaacat tactggaact ctatcctgtt 300
agggatcttc tgagcttgtt tccctgctgg gtgggacaga agacaaagga gaagggangg 360
tctacaanaa gcagcccttc tttgtcctct ggggttaatg agcttgacct ananttcatg 420
gaganaccan aagcctctga tttttaattt ccntnaaatg tttgaagtnt atatntacat 480
atatatattt ctttnaatnt ttgagtcttt gatatgtctt aaaatccant ccctctgccn 540
gaaacctgaa ttaaaaccat gaanaaaaat gtttncctta aagatgttan taattaattg 600
aaacttgaaa aaaaaaaaaa aa 622

<210> 58
<211> 433
<212> DNA
<213> Homo sapien

<400> 58
gaacaaattc tgattggtta tgtaccgtca aaagacttga agaaatttca tgattttgca 60
gtgtggaagc gttgaaaatt gaaagttact gcttttccac ttgctcatat agtaaaggga 120
tcctttcagc tgccagtgtt gaataatgta tcatccagag tgatgttatc tgtgacagtc 180
accagcttta agctgaacca ttttatgaat accaaataaa tagacctctt gtactgaaaa 240
catatttgtg actttaatcg tgctgcttgg atagaaatat ttttactggt tcttctgaat 300
tgacagtaaa cctgtccatt atgaatggcc tactgttcta ttatttgttt tgacttgaat 360
ttatccacca aagacttcat ttgtgtatca tcaataaagt tgtatgtttc aactgaaaaa 420
aaaaaaaaaa aaa 433

<210> 59
<211> 649
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(649)
<223> n = A,T,C or G

<400> 59
actagttatt atctgacttt cnggttataa tcattctaat gagtgtgaag tagcctctgg 60
tgtcatttgg atttgcattt ctctgatgag tgatgctatc aagcaccttt gctggtgctg 120
ttggccatat gtgtatgttc cctggagaag tgtctgtgct gagccttggc ccacttttta 180
attaggcgtn tgtcttttta ttactgagtt gtaaganttc tttatatatt ctggattcta 240
gacccttatc agatacatgg tttgcaaata ttttctccca ttctgtgggt tgtgttttca 300
ctttatcgat aatgtcctta gacatataat aaatttgtat tttaaaagtg acttgatttg 360
ggctgtgcaa ggtgggctca cgcttgtaat cccagcactt tgggagactg aggtgggtgg 420
atcatatgan gangctagga gttcgaggtc agcctggcca gcatagcgaa aacttgtctc 480
tacnaaaaat acaaaaatta gtcaggcatg gtggtgcacg tctgtaatac cagcttctca 540
ggangctgan gcacaaggat cacttgaacc ccagaangaa gangttgcag tganctgaag 600
atcatgccag ggcaacaaaa atgagaactt gtttaaaaaa aaaaaaaaa 649

<210> 60
<211> 423
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(423)
<223> n = A,T,C or G

<400> 60
actagttcag gccttccagt tcactgacaa acatggggaa gtgtgcccag ctggctggaa 60
acctggcagt gataccatca agcctgatgt ccaaaagagc aaagaatatt tctccaagca 120
gaagtgagcg ctgggctgtt ttagtgccag gctgcggtgg gcagccatga gaacaaaacc 180
tcttctgtat ttttttttc cattagtana acacaagact cngattcagc cgaattgtgg 240
tgtcttacaa ggcagggctt tcctacaggg ggtgganaaa acagcctttc ttcctttggt 300
aggaatggcc tgagttggcg ttgtgggcag gctactggtt tgtatgatgt attagtagag 360
caacccatta atcttttgta gtttgtatna aacttganct gagaccttaa acaaaaaaaa 420
aaa 423

<210> 61
<211> 423
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(423)
<223> n = A,T,C or G

<400> 61
cgggactgga atgtaaagtg aagttcggag ctctgagcac gggctcttcc cgccgggtcc 60
tccctcccca gaccccagag ggagaggccc accccgccca gccccgcccc agcccctgct 120
caggtctgag tatggctggg agtcgggggc cacaggcctc tagctgtgct gctcaagaag 180
actggatcag ggtanctaca agtggccggg ccttgccttt gggattctac cctgttccta 240
atttggtgtt ggggtgcggg gtccctggcc ccctttttcca cactncctcc ctccngacag 300
caacctccct tggggcaatt gggcctggnt ctccncccgn tgttgcnacc ctttgttggt 360
ttaaggnctt taaaaatgtt annttttccc ntgccngggt taaaaaagga aaaaactnaa 420
aaa 423

<210> 62
<211> 683
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(683)
<223> n = A,T,C or G

<400> 62
gctggagagg ggtacggact ttcttggagt tgtcccaggt tggaatgaga ctgaactcaa 60
gaagagaccc taagagactg gggaatggtt cctgccttca ggaaagtgaa agacgcttag 120
gctgtcaaca cttaaaggaa gtccccttga agcccagagt ggacagacta gacccattga 180

tggggccact ggccatggtc cgtggacaag acattccngt gggccatggc acaccggggg 240
ggatcaaaat gtgtacttgt ggggtctcgc cccttgccaa aaccaaacca ntcccactcc 300
tgtcnttgga ctttcttccc attccctcct ccccaaatgc acttcccctc ctccctctgc 360
ccctcctgtg tttttggaat tctgtttccc tcaaaattgt taatttttta nttttngacc 420
atgaacttat gtttggggtc nangttcccc ttnccaatgc atactaatat attaatggtt 480
atttattttt gaaatatttt ttaatgaact tggaaaaaat tnntggaatt tccttncttc 540
cnttttnttt gggggggggtg gggggntggg ttaaaatttt tttggaancc cnatnggaaa 600
ttnttacttg gggcccccct naaaaaantn anttccaatt cttnnatngc ccctnttccn 660
ctaaaaaaaa ananannaaa aan 683

<210> 63
<211> 731
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

<400> 63
actagtcata aagggtgtgc gcgtcttcga cgtggcggtc ttggcgccac tgctgcgaga 60
cccggccctg gacctcaagg tcatccactt ggtgcgtgat ccccgcgcgg tggcgagttc 120
acggatccgc tcgcgccacg gcctcatccg tgagagccta caggtggtgc gcagccgaga 180
ccgcgagctc accgcatgcc cttcttggag gccgcgggcc acaagcttgg cgcccanaaa 240
gaaggcgtng ggggcccgca aantaccacg ctctgggcgc tatggaangt cctcttgcaa 300
taatattggt tnaaaanctg canaanagcc cctgcanccc cctgaactgg gntgcagggc 360
cncttacctn gtttggntgc ggttacaaag aacctgtttn ggaaaaccct nccnaaaacc 420
ttccgggaaa attntncaaa tttttnttgg ggaattnttg ggtaaacccc ccnaaaatgg 480
gaaacntttt tgccctnnaa antaaaccat tnggttccgg gggccccccc ncaaaaccct 540
ttttttnttt tttntgcccc cantnncccc ccggggcccc ttttttttngg ggaaaanccc 600
ccccccctncc nanantttta aaagggnggg anaatttttn nttncccccc gggncccccn 660
ggngntaaaa nggtttcncc cccccgaggg gnggggnnnc ctcnnaaacc cntntcnnna 720
ccncnttttn n 731

<210> 64
<211> 313
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(313)
<223> n = A,T,C or G

<400> 64
actagttgtg caaaccacga ctgaagaaag acgaaaagtg ggaaataact tgcaacgtct 60
gttagagatg gttgctacac atgttgggtc tgtagagaaa catcttgagg agcagattgc 120
taaagttgat agagaatatg aagaatgcat gtcagaagat ctctcggaaa atattaaaga 180
gattagagat aagtatgaga agaaagctac tctaattaag tcttctgaag aatgaagatn 240
aaatgttgat catgtatata tatccatagt gaataaaatt gtctcagtaa agttgtaaaa 300
aaaaaaaaaa aaa 313

<210> 65

<211> 420
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(420)
<223> n = A,T,C or G

<400> 65
actagttccc tggcaggcaa gggcttccaa ctgaggcagt gcatgtgtgg cagagagagg 60
caggaagctg gcagtggcag cttctgtgtc tagggagggg tgtggctccc tccttccctg 120
tctgggaggt tggagggaag aatctaggcc ttagcttgcc ctcctgccac ccttcccctt 180
gtagatactg ccttaacact ccctcctctc tcagctgtgg ctgccaccca agccaggttt 240
ctccgtgctc actaatttat ttccaggaaa ggtgtgtgga agacatgagc cgtgtataat 300
atttgtttta acattttcat tgcaagtatt gaccatcatc cttggttgtg tatcgttgta 360
acacaaatta atgatattaa aaagcatcca aacaaagccn annnnnaana nnannngaaa 420

<210> 66
<211> 676
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(676)
<223> n = A,T,C or G

<400> 66
actagtttcc tatgatcatt aaactcattc tcagggttaa gaaaggaatg taaatttctg 60
cctcaatttg tacttcatca ataagttttt gaagagtgca gatttttagt caggtcttaa 120
aaataaactc acaaatctgg atgcatttct aaattctgca aatgtttcct ggggtgactt 180
aacaaggaat aatcccacaa tatacctagc tacctaatac atggagctgg ggctcaaccc 240
actgttttta aggatttgcg cttacttgtg gctgaggaaa aataagtagt tccgagggaa 300
gtagttttta aatgtgagct tatagatngg aaacagaata tcaacttaat tatggaaatt 360
gttagaaacc tgttctcttg ttatctgaat cttgattgca attactattg tactggatag 420
actccagccc attgcaaagt ctcagatatc ttanctgtgt agttgaattc cttggaaatt 480
ctttttaaga aaaaattgga gtttnaaaga aataaacccc tttgttaaat gaagcttggc 540
tttttggtga aaaanaatca tcccgcaggg cttattgttt aaaaanggaa ttttaagcct 600
ccctggaaaa anttgttaat taaatgggga aaatgntggg naaaaattat ccgttagggt 660
ttaaagggaa aactta 676

<210> 67
<211> 620
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(620)
<223> n = A,T,C or G

<400> 67
caccattaaa gctgcttacc aagaacttcc ccagcatttt gacttccttg tttgatagct 60

gaattgtgag caggtgatag aagagccttt ctagttgaac atacagataa tttgctgaat 120
acattccatt taatgaaggg gttacatctg ttacgaagct actaagaagg agcaagagca 180
taggggaaaa aaatctgatc agaacgcatc aaactcacat gtgccccctc tactacaaac 240
agattgtagt gctgtggtgg tttattccgt tgtgcagaac ttgcaagctg agtcactaaa 300
cccaaagaga ggaaattata ggttagttaa acattgtaat cccaggaact aagtttaatt 360
cacttttgaa gtgttttgtt ttttatttt ggtttgtctg atttactttg ggggaaaang 420
ctaaaaaaaa agggatatca atctctaatt cagtgcccac taaaagttgt ccctaaaaag 480
tctttactgg aanttatggg acttttaag ctccaggtnt tttggtcctc caaattaacc 540
ttgcatgggc cccttaaaat tgttgaangg cattcctgcc tctaagtttg gggaaaattc 600
ccccnttttn aaaatttgga 620

<210> 68
<211> 551
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(551)
<223> n = A,T,C or G

<400> 68
actagtagct ggtacataat cactgaggag ctatttctta acatgctttt atagaccatg 60
ctaatgctag accagtattt aagggctaat ctcacacctc cttagctgta agagtctggc 120
ttagaacaga cctctctgtg caataacttg tggccactgg aaatccctgg gccggcattt 180
gtattggggt tgcaatgact cccaagggcc aaaagagtta aaggcacgac tgggatttct 240
tctgagactg tggtgaaact ccttccaagg ctgagggggt cagtangtgc tctgggaggg 300
actcggcacc actttgatat tcaacaagcc acttgaagcc caattataaa attgttattt 360
tacagctgat ggaactcaat ttgaaccttc aaaactttgt tagtttatcc tattatattg 420
ttaaacctaa ttacatttgt ctagcattgg atttggttcc tgtngcatat gtttttttcn 480
cctatgtgct ccccctcccc nnatcttaat ttaaaccnca attttgcnat tcnccnnnnn 540
nannnannna a 551

<210> 69
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 69
cagaaatgga aagcagagtt ttcatttctg tttataaacg tctccaaaca aaaatggaaa 60
gcagagtttt cattaaatcc ttttaccttt tttttttctt ggtaatcccc tcaaataaca 120
gtatgtggga tattgaatgt taaagggata tttttttcta ttatttttat aattgtacaa 180
aattaagcaa atgttaaaag ttttatatgc tttattaatg ttttcaaaag gtatnataca 240
tgtgatacat tttttaagct tcagttgctt gtcttctggt actttctgtt atgggctttt 300
ggggagccan aaaccaatct acnatctctt tttgtttgcc aggacatgca ataaaattta 360
aaaaataaat aaaaactatt nagaaattga aaaaaa 396

<210> 70
<211> 536

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(536)
<223> n = A,T,C or G

<400> 70
actagtgcaa aagcaaatat aaacatcgaa aaggcgttcc tcacgttagc tgaagatatc 60
cttcgaaaga cccctgtaaa agagcccaac agtgaaaatg tagatatcag cagtggagga 120
ggcgtgacag gctggaagag caaatgctgc tgagcattct cctgttccat cagttgccat 180
ccactacccc gttttctctt cttgctgcaa aataaaccac tctgtccatt tttaactcta 240
aacagatatt tttgtttctc atcttaacta tccaagccac ctattttatt tgttctttca 300
tctgtgactg cttgctgact ttatcataat tttcttcaaa caaaaaaatg tatagaaaaa 360
tcatgtctgt gacttcattt ttaaatgnta cttgctcagc tcaactgcat ttcagttgtt 420
ttatagtcca gttcttatca acattnaaac ctatngcaat catttcaaat ctattctgca 480
aattgtataa gaataaaagt tagaatttaa caattaaaaa aaaaaaaaaa aaaaaa 536

<210> 71
<211> 865
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(865)
<223> n = A,T,C or G

<400> 71
gacaaagcgt taggagaaga anagaggcag ggaanactnc ccaggcacga tggccncctt 60
cccaccagca accagcgccc cccaccagcc cccaggcccg gacgacgaag actccatcct 120
ggattaatct nacctctntc gcctgnccca ttcctacctc ggaggtggag gccggaaagg 180
tcncaccaag aganaanctg ctgccaacac caaccgcccc agccctggcg ggcacganag 240
gaaactggtg accaatctgc agaattctna gaggaanaag cnaggggccc cgcgctnaga 300
cagagctgga tatgangcca gaccatggac nctacncccn ncaatncana cgggactgcg 360
gaagatggan gacccncgac nngatcaggc cngctnncca nccccccacc cctatgaatt 420
attcccgctg aangaatctc tgannggctt ccannaaagc gcctccccnc cnaacgnaan 480
tncaacatng ggattanang ctgggaactg naaggggcaa ancctnnaat atccccagaa 540
acaanctctc ccnaanaaac tggggcncct catnggtggn accaactatt aactaaaccg 600
cacgccaagn aantataaaa gggggggccc tccncggnng acccccttttt gtcccttaat 660
ganggttatc cnccttgcgt accatggtnc ccnnttctgt ntgnatgttt ccnctcccct 720
ccncctatnt cnagccgaac tcnnatttnc ccgggggtgc natcnantng tncnccttta 780
ttngttgncc cngccctttc cgncggaacn cgtttccccg ttantaacgg cacccggggn 840
aagggtgntt ggcccccctcc ctccc 865

<210> 72
<211> 560
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(560)

<223> n = A,T,C or G

<400> 72
cctggacttg tcttggttcc agaacctgac gacccggcga cggcgacgtc tcttttgact 60
aaaagacagt gtccagtgct ccngcctagg agtctacggg gaccgcctcc cgcgccgcca 120
ccatgcccaa cttctctggc aactggaaaa tcatccgatc ggaaaacttc gangaattgc 180
tcnaantgct gggggtgaat gtgatgctna ngaanattgc tgtggctgca gcgtccaagc 240
cagcagtgga gatcnaacag gagggagaca ctttctacat caaaacctcc accaccgtgc 300
gcaccacaaa gattaacttc nnngttgggg aggantttga ggancaaact gtggatngga 360
ngcctgtnaa aacctggtga aatgggagaa tganaataaa atggtctgtg ancanaaact 420
cctgaaagga gaaggccccc anaactcctg gaccngaaaa actgacccnc cnatngggga 480
actgatnctt gaaccctgaa cgggcgggat gancctttt tnttgccncc naangggttc 540
tttccntttc cccaaaaaaa 560

<210> 73
<211> 379
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(379)
<223> n = A,T,C or G

<400> 73
ctggggancc ggcggtnngc nccatntcnn gncgcgaagg tggcaataaa aanccnctga 60
aaccgcncaa naaacatgcc naagatatgg acgaggaaga tngngctttc nngnacaanc 120
gnanngagga acanaacaaa ctcnangagc tctcaagcta atgccgcggg gaaggggccc 180
ttggccacnn gtggaattaa gaaatctggc aaannngtann tgttccttgt gcctnangag 240
ataagngacc ctttatttca tctgtattta aacctctctn ttccctgnca taacttcttt 300
tnccacgtan agntggaant anttgttgtc ttggactgtt gtncatttta gannaaactt 360
ttgttcaaaa aaaaaataa 379

<210> 74
<211> 437
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(437)
<223> n = A,T,C or G

<400> 74
actagttcag actgccacgc caaccccaga aaatacccca catgccagaa aagtgaagtc 60
ctaggtgttt ccatctatgt ttcaatctgt ccatctacca ggcctcgcga taaaaacaaa 120
acaaaaaaac gctgccaggt tttanaagca gttctggtct caaaaccatc aggatcctgc 180
caccagggtt cttttgaaat agtaccacat gtaaaaggga atttggcttt cacttcatct 240
aatcactgaa ttgtcaggct ttgattgata attgtagaaa taagtagcct tctgttgtgg 300
gaataagtta taatcagtat tcatctcttt gtttttttgtc actcttttct ctctnattgt 360
gtcatttgta ctgtttgaaa aatatttctt ctataaaatt aaactaacct gccttaaaaa 420
aaaaaaaaaa aaaaaaa 437

<210> 75

<211> 579
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(579)
<223> n = A,T,C or G

<400> 75
ctccgtcgcc gccaagatga tgtgcggggc gccctccgcc acgcagccgg ccaccgccga 60
gacccagcac atcgccgacc aggtgaggtc ccagcttgaa gagaaagaaa acaagaagtt 120
ccctgtgttt aaggccgtgt cattcaagag ccaggtggtc gcggggacaa actacttcat 180
caaggtgcac gtcggcgacg aggacttcgt acacctgcga gtgttccaat ctctccctca 240
tgaaaacaag cccttgacct tatctaacta ccagaccaac aaagccaagc atgatgagct 300
gacctatttc tgatcctgac tttggacaag gcccttcagc cagaagactg acaaagtcat 360
cctccgtcta ccagagcgtg cacttgtgat cctaaaataa gcttcatctc cgggctgtgc 420
ccttggggtg gaaggggcan gatctgcact gcttttgcat ttctcttcct aaatttcatt 480
gtgttgattc tttccttcca ataggtgatc ttnattactt tcagaatatt ttccaaatna 540
gatatatttt naaaatcctt aaaaaaaaaa aaaaaaaaa 579

<210> 76
<211> 666
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(666)
<223> n = A,T,C or G

<400> 76
gtttatccta tctctccaac cagattgtca gctccttgag ggcaagagcc acagtatatt 60
tccctgtttc ttccacagtg cctaataata ctgtggaact aggttttaat aatttttaa 120
ttgatgttgt tatgggcagg atggcaacca gaccattgtc tcagagcagg tgctggctct 180
ttcctggcta ctccatgttg gctagcctct ggtaacctct tacttattat cttcaggaca 240
ctcactacag ggaccaggga tgatgcaaca tccttgtctt tttatgacag gatgtttgct 300
cagcttctcc aacaataaaa agcacgtggt aaaacacttg cggatattct ggactgtttt 360
taaaaaatat acagtttacc gaaaatcata ttatcttaca atgaaaagga ntttatagat 420
cagccagtga acaacctttt cccaccatac aaaaattcct tttcccgaan gaaaanggct 480
ttctcaataa ncctcacttt cttaanatct tacaagatag ccccganatc ttatcgaaac 540
tcattttagg caaatatgan ttttattgtn cgttacttgt ttcaaaattt ggtattgtga 600
atatcaatta ccacccccat ctcccatgaa anaaanggga aanggtgaan ttcntaancg 660
cttaaa 666

<210> 77
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 77
ctgcagcccg ggggatccac taatctacca nggttatttg gcagctaatt ctanatttgg 60
atcattgccc aaagttgcac ttgctggtct cttgggattt ggccttggaa aggtatcata 120
catanganta tgccanaata aattccattt ttttgaaaat canctccntg gggctggttt 180
tggtccacag cataacangc actgcctcct tacctgtgag gaatgcaaaa taaagcatgg 240
attaagtgag aagggagact ctcagccttc agcttcctaa attctgtgtc tgtgactttc 300
gaagtttttt aaacctctga atttgtacac atttaaaatt tcaagtgtac tttaaaataa 360
aatacttcta atgggaacaa aaaaaaaaaa aaaaaa 396

<210> 78
<211> 793
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(793)
<223> n = A,T,C or G

<400> 78
gcatcctagc cgccgactca cacaaggcag gtgggtgagg aaatccagag ttgccatgga 60
gaaaattcca gtgtcagcat tcttgctcct tgtggccctc tcctacactc tggccagaga 120
taccacagtc aaacctggag ccaaaaagga cacaaaggac tctcgaccca aactgcccca 180
gaccctctcc agaggttggg gtgaccaact catctggact cagacatatg aagaagctct 240
atataaatcc aagacaagca acaaaccctt gatgattatt catcacttgg atgagtgccc 300
acacagtcna gctttaaaga aagtgtttgc tgaaaataaa gaaatccaga aattggcaga 360
gcagtttgtc ctcctcaatc tggtttatga aacaactgac aaacaccttt ctcctgatgg 420
ccagtatgtc ccaggattat gtttgttgac ccatctctga cagttgaagc cgatatcctg 480
ggaagatatt cnaaccgtct ctatgcttac aaactgcaga tacgctctgt tgcttgacac 540
atgaaaaagc tctcaagttg ctnaaaatga attgtaagaa aaaaaatctc cagccttctg 600
tctgtcggct tgaaaattga aaccagaaaa atgtgaaaaa tggctattgt ggaacanatn 660
gacacctgat taggttttgg ttatgttcac cactattttt aanaaaanan nttttaaaat 720
ttggttcaat tntctttttn aaacaatntg tttctacntt gnganctgat ttctaaaaaa 780
aataatnttt ggc 793

<210> 79
<211> 456
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(456)
<223> n = A,T,C or G

<400> 79
actagtatgg ggtgggaggc cccacccttc tcccctaggc gctgttcttg ctccaaaggg 60
ctccgtggag agggactggc agagctgang ccacctgggg ctggggatcc cactcttctt 120
gcagctgttg agcgcaccta accactggtc atgcccccac ccctgctctc cgcacccgct 180
tcctcccgac cccangacca ggctacttct cccctcctct tgcctccctc ctgcccctgc 240
tgcctctgat cgtangaatt gangantgtc ccgccttgtg gctganaatg gacagtggca 300
ggggctggaa atgggtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gcnccccccc 360
tgcaagaccg agattgaggg aaancatgtc tgctgggtgt gaccatgttt cctctccata 420

aantncccct gtgacnctca naaaaaaaaa aaaaaa 456

<210> 80
<211> 284
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(284)
<223> n = A,T,C or G

<400> 80
ctttgtacct ctagaaaaga taggtattgt gtcatgaaac ttgagtttaa attttatata 60
taaaactaaa agtaatgctc actttagcaa cacatactaa aattggaacc atactgagaa 120
gaatagcatg acctccgtgc aaacaggaca agcaaatttg tgatgtgttg attaaaaaga 180
aataaataaa tgtgtatatg tgtaacttgt atgtttatgt ggaatacaga ttgggaaata 240
aaatgtattt cttactgtga aaaaaaaaaa aaaaaaaaaa aana 284

<210> 81
<211> 671
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(671)
<223> n = A,T,C or G

<400> 81
gccaccaaca ttccaagcta ccctgggtac ctttgtgcag tagaagctag tgagcatgtg 60
agcaagcggt gtgcacacgg agactcatcg ttataattta ctatctgcca agagtagaaa 120
gaaaggctgg ggatatttgg gttggcttgg ttttgatttt ttgcttgttt gtttgttttg 180
tactaaaaca gtattatctt ttgaatatcg tagggacata agtatataca tgttatccaa 240
tcaagatggc tagaatggtg cctttctgag tgtctaaaac ttgacacccc tggtaaatct 300
ttcaacacac ttccactgcc tgcgtaatga agttttgatt catttttaac cactggaatt 360
tttcaatgcc gtcattttca gttagatnat tttgcacttt gagattaaaa tgccatgtct 420
atttgattag tcttatttttt ttatttttac aggcttatca gtctcactgt tggctgtcat 480
tgtgacaaag tcaaataaac ccccnaggac aacacacagt atgggatcac atattgtttg 540
acattaagct ttggccaaaa aatgttgcat gtgttttacc tcgacttgct aaatcaatan 600
canaaaggct ggctnataat gttggtggtg aaataattaa tnantaacca aaaaaaaaan 660
aaaaaaaaaa a 671

<210> 82
<211> 217
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(217)
<223> n = A,T,C or G

<400> 82

ctgcagatgt ttcttgaatg ctttgtcaaa ttaanaaagt taaagtgcaa taatgtttga 60
agacaataag tggtggtgta tcttgtttct aataagataa acttttttgt ctttgcttta 120
tcttattagg gagttgtatg tcagtgtata aaacatactg tgtggtataa caggcttaat 180
aaattcttta aaaggaaaaa aaaaaaaaaa aaaaaaa 217

<210> 83
<211> 460
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(460)
<223> n = A,T,C or G

<400> 83
cgcgagtggg agcaccagga tctcgggctc ggaacgagac tgcacggatt gttttaagaa 60
aatggcagac aaaccagaca tgggggaaat cgccagcttc gatnaggcca agctgaanaa 120
aacggagacg caggagaaga acaccctgcc gaccaaagag accattgagc angagaagcg 180
gagtgaaatt tcctaagatc ctggaggatt tcctaccccc gtcctcttcg agaccccagt 240
cgtgatgtgg aggaagagcc acctgcaaga tggacacgag ccacaagctg cactgtgaac 300
ctgggcactc cgcgccgatg ccaccggcct gtgggtctct gaagggaccc cccccaatcg 360
gactgccaaa ttctccggtt tgccccggga tattatacaa nattatttgt atgaataatg 420
annataaaac acacctcgtg gcancaaana aaaaaaaaaa 460

<210> 84
<211> 323
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(323)
<223> n = A,T,C or G

<400> 84
tggtggatct tggctctgtg gagctgctgg gacgggatct aaaagactat tctggaagct 60
gtggtccaan gcattttgct ggcttaacgg gtcccggaac aaaggacacc agctctctaa 120
aattgaagtt tacccganat aacaatcttt tgggcagaga tgcctatttt aacaaacncc 180
gtccctgcgc aacaacnaac aatctctggg aaataccggc catgaacntg ctgtctcaat 240
cnancatctc tctagctgac cgatcatatc gtcccagatt actacanatc ataataattg 300
atttcctgta naaaaaaaaa aaa 323

<210> 85
<211> 771
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(771)
<223> n = A,T,C or G

<400> 85

aaactgggta ctcaacactg agcagatctg ttctttgagc taaaaaccat gtgctgtacc 60
aanagtttgc tcctggctgc tttgatgtca gtgctgctac tccacctctg cggcgaatca 120
gaagcaagca actttgactg ctgtcttgga tacacagacc gtattcttca tcctaaattt 180
attgtgggct tcacacggca gctggccaat gaaggctgtg acatcaatgc tatcatcttt 240
cacacaaaga aaaagttgtc tgtgtgcgca aatccaaaac agacttgggt gaaatatatt 300
gtgcgtctcc tcagtaaaaa agtcaagaac atgtaaaaac tgtggctttt ctggaatgga 360
attggacata gcccaagaac agaaagaact tgctggggtt ggaggtttca cttgcacatc 420
atgganggtt tagtgcttat cttatttgtg cctcctggac ttgtccaatt natgaagtta 480
atcatattgc atcatanttt gctttgttta acatcacatt naaattaaac tgtatttttat 540
gttatttata gctntaggtt ttctgtgttt aacttttttat acnaantttc ctaaactatt 600
ttggtntant gcaanttaaa aattatattt ggggggggaa taaatattgg antttctgca 660
gccacaagct ttttttaaaa aaccantaca nccnngttaa atggtnggtc ccnaatggtt 720
tttgcttttn antagaaaat ttnttagaac natttgaaaa aaaaaaaaaa a 771

<210> 86
<211> 628
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(628)
<223> n = A,T,C or G

<400> 86
actagtttgc tttacatttt tgaaaagtat tatttttgtc caagtgctta tcaactaaac 60
cttgtgttag gtaagaatgg aatttattaa gtgaatcagt gtgacccttc ttgtcataag 120
attatcttaa agctgaagcc aaaatatgct tcaaaagaaa angactttat tgttcattgt 180
agttcataca ttcaaagcat ctgaactgta gtttctatag caagccaatt acatccataa 240
gtggagaang aaatagatta atgtcnaagt atgattggtg gagggagcaa ggttgaagat 300
aatctggggt tgaaattttc tagttttcat tctgtacatt tttagttnga catcagattt 360
gaaatattaa tgtttacctt tcaatgtgtg gtatcagctg gactcantaa cacccctttc 420
ttccctnggg gatggggaat ggattattgg aaaatggaaa gaaaaaagta cttaaagcct 480
tcctttcnca gtttctggct cctaccctac tgatttancc agaataagaa aacatttat 540
catcntctgc tttattccca ttaatnaant tttgatgaat aaatctgctt ttatgcnnac 600
ccaaggaatt nagtggnttc ntcnttgt 628

<210> 87
<211> 518
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(518)
<223> n = A,T,C or G

<400> 87
ttttttattt tttttagaga gtagttcagc ttttatttat aaatttattg cctgttttat 60
tataacaaca ttatactgtt tatggtttaa tacatatggt tcaaaatgta taatacatca 120
agtagtacag ttttaaaatt ttatgcttaa aacaagtttt gtgtaaaaaa tgcagataca 180
ttttacatgg caaatcaatt tttaagtcat cctaaaaatt gatttttttt tgaaatttaa 240
aaacacattt aatttcaatt tctctcttat ataaccttta ttactatagc atggtttcca 300
ctacagttta acaatgcagc aaaattccca tttcacggta aattgggttt taagcggcaa 360

ggttaaaatg ctttgaggat cctnaatacc ctttgaactt caaatgaagg ttatggttgt 420
naatttaacc ctcatgccat aagcagaagc acaagtttag ctgcattttg ctctaaactg 480
taaaancgag ccccccgttg aaaaagcaaa agggaccc 518

<210> 88
<211> 1844
<212> DNA
<213> Homo sapien

<400> 88
gagacagtga atcctagtat caaaggattt ttggcctcag aaaaagttgt tgattatttt 60
tattttattt tatttttcga gactccgtct caaaaaaaaa aaaaaaaaaa agaatcacaa 120
ggtatttgct aaagcatttt gagctgcttg gaaaaaggga agtagttgca gtagagtttc 180
ttccatcttc ttggtgctgg gaagccatat atgtgtcttt tactcaagct aaggggtata 240
agcttatgtg ttgaatttgc tacatctata tttcacatat tctcacaata agagaatttt 300
gaaatagaaa tatcatagaa catttaagaa agtttagtat aaataatatt ttgtgtgttt 360
taatcccttt gaagggatct atccaaagaa aatattttac actgagctcc ttcctacacg 420
tctcagtaac agatcctgtg ttagtctttg aaaatagctc atttttaaa tgtcagtgag 480
tagatgtagc atacatatga tgtataatga cgtgtattat gttaacaatg tctgcagatt 540
ttgtaggaat acaaaacatg gccttttta taagcaaaac gggccaatga ctagaataac 600
acatagggca atctgtgaat atgtattata agcagcattc cagaaaagta gttggtgaaa 660
taattttcaa gtcaaaaagg gatatggaaa gggaattatg agtaacctct atttttaag 720
ccttgctttt aaattaaacg ctacagccat ttaagccttg aggataataa agcttgagag 780
taataatgtt aggttagcaa aggtttagat gtatcacttc atgcatgcta ccatgatagt 840
aatgcagctc ttcgagtcat ttctggtcat tcaagatatt cacccttttg cccatagaaa 900
gcaccctacc tcacctgctt actgacattg tcttagctga tcacaagatc attatcagcc 960
tccattattc cttactgtat ataaaataca gagttttata ttttcctttc ttcgtttttc 1020
accatattca aaacctaaat ttgtttttgc agatggaatg caaagtaatc aagtgttcgt 1080
gctttcacct agaagggtgt ggtcctgaag gaaagaggtc cctaaatatc ccccaccctg 1140
ggtgctcctc cttccctggt accctgacta ccagaagtca ggtgctagag cagctggaga 1200
agtgcagcag cctgtgcttc cacagatggg ggtgctgctg caacaaggct ttcaatgtgc 1260
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ccaatttacc gtgaaatggg aattttgctg cattgttaaa ctgtagtgga aaccatgcta 1560
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aaaatcaatc tttaggatga cttaaaaatt gatttgccat gtaaaatgta tctgcatttt 1680
ttacacaaaa cttgttttaa gcataaaatt ttaaaactgt actacttgat gtattataca 1740
ttttgaacca tatgtattaa accataaaca gtataatgtt gttataataa aacaggcaat 1800
aaatttataa ataaaagctg aaaaaaaaaa aaaaaaaaaa aaaa 1844

<210> 89
<211> 523
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(523)
<223> n = A,T,C or G

<400> 89
ttttttttttt ttttttttagt caatccacat ttattgatca cttattatgt accaggcact 60

gggataaaga tgactgttag tcactcacag taaggaagaa aactagcaaa taagacgatt 120
acaatatgat gtagaaaatg ctaagccaga gatatagaaa ggtcctattg ggtccttctg 180
tcaccttgtc tttccacatc cctacccttc acaggccttc cctccagctt cctgcccccg 240
ctccccactg cagatcccct gggattttgc ctagagctaa acgagganat gggccccctg 300
gccctggcat gacttgaacc caaccacaga ctgggaaagg gagcctttcg anagtggatc 360
actttgatna gaaaacacat agggaattga agagaaantc cccaaatggc cacccgtgct 420
ggtgctcaag aaaagtttgc agaatggata aatgaaggat caagggaatt aatanatgaa 480
taattgaatg gtggctcaat aagaatgact ncnttgaatg acc 523

<210> 90
<211> 604
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(604)
<223> n = A,T,C or G

<400> 90
ccagtgtggt ggaatgcaaa gattaccccg gaagctttcg agaagctggg attccctgca 60
gcaaaggaaa tagccaatat gtgtcgtttc tatgaaatga agccagaccg agatgtcaat 120
ctcacccacc aactaaatcc caaagtcaaa agcttcagcc agtttatctc agagaaccag 180
gggagccttc aagggcatgt agaaaatcag ctgttcagat aggcctctgc accacacagc 240
ctctttcctc tctgatcctt ttcctcttta cggcacaaca ttcatgtttg acagaacatg 300
ctggaatgca attgtttgca acaccgaagg atttcctgcg gtcgcctctt cagtaggaag 360
cactgcattg gtgataggac acggtaattt gattcacatt taacttgcta gttagtgata 420
aggggtggta cacctgtttg gtaaaatgag aagcctcgga aacttgggag cttctctcct 480
accactaatg gggagggcag attattactg ggatttctcc tggggtgaat taatttcaag 540
ccctaattgc tgaaattccc ctnggcaggc tccagttttc tcaactgcat tgcaaaattc 600
cccc 604

<210> 91
<211> 858
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(858)
<223> n = A,T,C or G

<400> 91
ttttttttt ttttttttta tgattattat ttttttatt gatctttaca tcctcagtgt 60
tggcagagtt tctgatgctt aataaacatt tgttctgatc agataagtgg aaaaaattgt 120
catttcctta ttcaagccat gcttttctgt gatattctga tcctagttga acatacagaa 180
ataaatgtct aaaacagcac ctcgattctc gtctataaca ggactaagtt cactgtgatc 240
ttaaataagc ttggctaaaa tgggacatga gtggaggtag tcacacttca gcgaagaaag 300
agaatctcct gtataatctc accaggagat tcaacgaatt ccaccacact ggactagtgg 360
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gcccggtacc caattcgccc tatagtgagt cgtattacgc gcgctcactg gccgtcgttt 480
tacaacgtcg tgactgggaa aaccctggcg ttacccaact taatcgcctt gcagcacatc 540
ccccttcgc cagctggcgt aatagcgaan agcccgcacc gatcgccctt ncaacagttg 600
cgcagcctga atggcgaatg ggacgcgccc tgtagcggcg cattaaagcg cggcngggtg 660

tggnggntcc cccacgtgac cgntacactt ggcagcgcct tacgccggtc nttcgctttc 720
ttcccttcct ttctcgcacc gttcgccggg tttccccgnn agctnttaat cgggggnctc 780
cctttanggg tncnaattaa nggnttacng gaccttngan cccaaaaact ttgattaggg 840
ggaaggtccc cgaagggg 858

<210> 92
<211> 585
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(585)
<223> n = A,T,C or G

<400> 92
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tccactcatg tcccatttta gccaagctta tttaagatca cagtgaactt agtcctgtta 120
tagacgagaa tcgaggtgct gttttagaca tttatttctg tatgttcaac taggatcaga 180
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gaacaaatgt ttattaagca tcagaaactc tgccaacact gaggatgtaa agatcaataa 300
aaaaaataat aatcatnann naaanannan nngaagggcg gccgccaccg cggtggagct 360
ccagcttttg ttccctttag tgagggttaa ttgcgcgctt ggcgttaatc atggtcatag 420
ctgtttcctg tgtgaaattg ttatccggct cacaattccn cncaacatac gagccgggaa 480
gcntnangtg taaaagcctg ggggtgccta attgagtgag ctnactcaca ttaattgngt 540
tgcgctccac ttgcccgctt ttccantccg ggaaacctgt tcgnc 585

<210> 93
<211> 567
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(567)
<223> n = A,T,C or G

<400> 93
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agactgcggc tggggtgggc anggaaggga accgggggct gctgtgaagg atcttggaac 120
ttccctgtac ccaccttccc cttgcttcat gtttgtanag gaaccttgtg ccggccaagc 180
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attaaattgc tantgtttct ttgaannnnn nnnnnnnnnn nnnnnnnggg ggggncgccc 300
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gttaanccnt gggccaaanc tngttncccg tgntgaaatt gttnatcccc tcccaaattc 420
ccccccnncc ttccaaaccc ggaaancctn annntgttna ancccggggg gttgcctaan 480
ngnaattnaa ccnaaccccc ntttaaaatng nntttgcncn ccacnngccc cnctttccca 540
nttcggggaa aaccctntcc gtgccca 567

<210> 94
<211> 620
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(620)
<223> n = A,T,C or G

<400> 94
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catgtttatc ttttattatg ttttgtgaag ttgtgtcttt tcactaatta cctatactat 120
gccaatattt ccttatatct atccataaca tttatactac atttgtaana naatatgcac 180
gtgaaactta acactttata aggtaaaaat gaggtttcca anatttaata atctgatcaa 240
gttcttgtta tttccaaata gaatggactt ggtctgttaa gggctaagga gaagaggaag 300
ataaggttaa aagttgttaa tgaccaaaca ttctaaaaga aatgcaaaaa aaaagtttat 360
tttcaagcct tcgaactatt taaggaaagc aaaatcattt cctaaatgca tatcatttgt 420
gagaatttct cattaatatc ctgaatcatt catttcacta aggctcatgt tnactccgat 480
atgtctctaa gaaagtacta tttcatggtc caaacctggt tgccatantt gggtaaaggc 540
tttcccttaa gtgtgaaant atttaaaatg aaattttcct ctttttaaaa attctttana 600
agggttaagg gtgttgggga 620

<210> 95
<211> 470
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(470)
<223> n = A,T,C or G

<400> 95
ctcgaccttc tctgcacagc ggatgaaccc tgagcagctg aagaccagaa aagccactat 60
nactttntgc ttaattcang agcttacang attcttcaaa gagtgngtcc agcatccttt 120
gaaacatgag ttcttaccag cagaagcaga cctttacccc accacctcag cttcaacagc 180
agcaggtgaa acaacccatc cagcctccac ctnaggaaat atttgttccc acaaccaagg 240
agccatgcca ctcaaaggtt ccacaacctg naaacacaaa nattccagag ccaggctgta 300
ccaaggtccc tgagccaggg ctgtaccaan gtccctgagc caggttgtac caangtccct 360
gagccaggat gtaccaaggt ccctgancca ggttgtccaa ggtccctgag ccaggctaca 420
ccaagggcct gngccaggca gcatcaangt ccctgaccaa ggcttatcaa 470

<210> 96
<211> 660
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(660)
<223> n = A,T,C or G

<400> 96
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gcatttcttt tcattcgaat cttcagatga accctgagca gccgaagacc agaaaagcca 120
tgaagacttt ctgcttaatt caggggctta caggattctt cagagtgtgt gtgaacaaaa 180
gctttatagt acgtattttt aggatacaaa taagagagag actatggctt ggggtgagaa 240
tgtactgatt acaaggtcta cagacaatta agacacagaa acagatggga agagggtgnc 300

cagcatctgg nggttggctt ctcaagggct tgtctgtgca ccaaattact tctgcttggn 360
cttctgctga gctgggcctg gagtgaccgt tgaaggacat ggctctggta cctttgtgta 420
gcctgncaca ggaactttgg tgtatccttg ctcaggaact ttgatggcac ctggctcagg 480
aaacttgatg aagccttggt caagggacct tgatgcttgc tggctcaggg accttggngn 540
ancctgggct canggacctt tgncncaacc ttggcttcaa gggacccttg gnacatcctg 600
gcnnagggac ccttgggncc aaccctgggc ttnagggacc ctttggntnc nanccttggc 660

<210> 97
<211> 441
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(441)
<223> n = A,T,C or G

<400> 97
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agccttgcca gcctccacct caggaaccat gcatccccaa aaccaaggag ccctgccacc 180
ccaaggtgcc tgagccctgc caccccaaag tgcctgagcc ctgccagccc aaggttccag 240
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agcagaanac caagcagaag taatgtggtc cacagccatg cccttgagga gccggccacc 360
agatgctgaa tcccctatcc cattctgtgt atgagtccca tttgccttgc aattagcatt 420
ctgtctcccc caaaaaaaaa a 441

<210> 98
<211> 600
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(600)
<223> n = A,T,C or G

<400> 98
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gcagccctgc atcccacccc ctcagcttca gcagcagcag gtgaaacagc cttgccagcc 120
tccacctcag gaaccatgca tccccaaaac caaggagccc tgccacccca aggtgcctga 180
gccctgccac cccaaagtgc ctgagccctg ccagcccaag gttccagagc catgccaccc 240
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aaaagaatgt gctatgaagc tttctttcct acacactctg agtctctgaa tgaagctgaa 480
ggtcttaant acaganctag ttttcagctg ctcagaattc tctgaagaaa agatttaaga 540
tgaaaggcaa atgattcagc tccttattac cccattaaat tcnctttcaa ttccaaaaaa 600

<210> 99
<211> 667
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G

<400> 99
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accatttaaa aaaatcagtg aaggatttga gctgctcaat tcaggacaaa gcattcgaac 120
ggtcctgacg ttttgagatc caaagtggca ggaggtctgt gttgtcatgg tgaactggag 180
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tggagatttt taagagtttt aaccagctgc tgcagatata ttactcaaaa cagatatagc 480
gtataaagat atagtaaatg catctcctag agtaatattc acttaacaca ttggaaacta 540
ttatttttta gatttgaata tnaatgttat tttttaaaca cttgttatga gttacttggg 600
attacatttt gaaatcagtt cattccatga tgcanattac tgggattaga ttaagaaaga 660
cggaaaa 667

<210> 100
<211> 583
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(583)
<223> n = A,T,C or G

<400> 100
gttttgtttg taagatgatc acagtcatgt tacactgatc taaaggacat atatataacc 60
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tgtttttctg aagatcaatt agacattttg aaaatgattt aaagtgtttt ccttaatgtt 180
ctctgaaaac aagtttcttt tgtagtttta accaaaaaag tgccctttt gtcactggat 240
tctcctagca ttcatgattt ttttttcata caatgaaatt aaaattgcta aaatcatgga 300
ctggctttct ggttggattt caggtaagat gtgtttaagg ccagagcttt tctcagtatt 360
tgatttttt ccccaatatt tgatttttta aaaatataca catnggtgct gcatttatat 420
ctgctggttt aaaattctgt catatttcac ttctagcctt ttagttatgg caaatcatat 480
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attctatnaa ttgaantttt ggtactcnnc catatttgga tcc 583

<210> 101
<211> 592
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(592)
<223> n = A,T,C or G

<400> 101
gtggagacgt acaaagagca gccgctcaag acacctggga agaaaaagaa aggcaagccc 60
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ggagtgactg ggagtgggct agaaggggac cacctgtctg acacctccac aacgtcgctg 180
gagctcgatt cacggaggca ttgaaatttt cagcaganac cttccaagga catattgcag 240
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aaatgcattg gaataaaact gtctccccca ttgctctatg aaactgcaca ttggtcattg 360
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attttgtcca ttgatgtatt tattttgtaa atgtatcttg gtgctgctga atttctatat 480
tttttgtaca taatgcnttt anatatacct atcaagtttg ttgataaatg acncaatgaa 540
gtgncncnan ttggnggttg aatttaatga atgcctaatt ttattatccc aa 592

<210> 102
<211> 587
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(587)
<223> n = A,T,C or G

<400> 102
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gcttatgttt tctggaagaa agtggagacc nagtccttgg ctttagggct ccccggctgg 120
gggctgtgca ntccggtcag ggcgggaagg gaaatgcacc gctgcatgtg aacttacagc 180
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ttcctttgaa aaagggcaaa actgaaaagg gcttttccta naaaaagaaa aaccagggaa 480
ctttgccagg gcttcnntnt taccaaaacn ncttctcnng gatttttaat tccccattng 540
gcctccactt accnggggcn atgccccaaa attaanaatt tcccatc 587

<210> 103
<211> 496
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(496)
<223> n = A,T,C or G

<400> 103
anaggactgg ccctacntgc tctctctcgt cctacctatc aatgcccaac atggcagaac 60
ctgcanccct tggncactgc anatggaaac ctctcagtgt cttgacatca ccctacccnt 120
gcggtgggtc tccaccacaa ccactttgac tctgtggtcc ctgnanggtg gnttctcctg 180
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cccttaacat gatataatcc acccatgcaa ntngctactg gcccagctac catttaccat 300
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tgggctgacc gcaaaaggtg ccttacacac tggcccccac cctcaaccgt tgacncatca 420
gangcttgcc tcctccttct gattnncccc catgttggat atcagggtgc tcnagggatt 480
ggaaaagaaa caaaac 496

<210> 104
<211> 575

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(575)
<223> n = A,T,C or G

<400> 104
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ctatggangt ggtttcnggg gtggctcttg ccaactggga agaagccgtg gtgtctctac 120
ctgttcaact cngtttgtgt ctgggggatc aactnggggc tatggaagcg gctnaactgt 180
tgttttggtg gaagggctgg taattggctt tgggaagtng cttatngaag ttggcctngg 240
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ccnatgcngn aaacctcnac nnaacagcct gggcttccct cacctcgaaa aaagttgctc 420
ccccccccaaa aaaggncaan cccctcaann tggaangttg aaaaaatcct cgaatgggga 480
ncccnaaaac aaaaancccc ccntttcccn gnaanggggg aaataccncc cccccactta 540
cnaaaaccct tntaaaaaac ccccgggaa aaaaa 575

<210> 105
<211> 619
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(619)
<223> n = A,T,C or G

<400> 105
cactagtagg atagaaacac tgtgtcccga gagtaaggag agaagctact attgattaga 60
gcctaaccca ggttaactgc aagaagaggc gggatacttt cagctttcca tgtaactgta 120
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aagtggtggg gaaaaaaaa 619

<210> 106
<211> 506
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(506)
<223> n = A,T,C or G

<400> 106

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angtanagat gttctggata ccattanatn tgccccngt gtcagaggct catattgtgt 180
tatgtaaatg gtatntcatt cgctactatn antcaattng aaatanggtc tttgggttat 240
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gactgtggta ncccgcatcg gaaaaa 506

<210> 107
<211> 452
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(452)
<223> n = A,T,C or G

<400> 107
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ccactttaaa accaaaaaat tccccttgga aa 452

<210> 108
<211> 502
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 108
atcttcttcc cttaattagt tnttatttat ntattaaatt ttattgcatg tcctggcaaa 60
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ctccagaaca aaaacttntc aantctttca gctaaccgca tttgagctna ggccactcaa 420
aaactccatt agncccactt tctaanggtc tctanagctt actaancctt ttgacccctt 480
accctggnta ctcctgccct ca 502

<210> 109
<211> 1308
<212> DNA

<213> Homo sapien

<400> 109

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ggcatcttga ctgcaattgg catggtcctc ctggggaccc gaggagccac cgcttcccag     180
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ataagcaaac tcactaatga ttatgaactg aacataacca acaggctgtt tggagaaaaa     360
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<210> 110
<211> 391
<212> PRT
<213> Homo sapien

<400> 110

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            20                  25                  30
Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala
        35                  40                  45
Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
    50                  55                  60
Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Ile Glu Asn Thr Glu
65                  70                  75                  80
Ala Val His Gln Gln Phe Gln Lys Phe Leu Thr Glu Ile Ser Lys Leu
                85                  90                  95
Thr Asn Asp Tyr Glu Leu Asn Ile Thr Asn Arg Leu Phe Gly Glu Lys
            100                 105                 110
Thr Tyr Leu Phe Leu Gln Lys Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr
        115                 120                 125
His Ala Ser Leu Glu Pro Val Asp Phe Val Asn Ala Ala Asp Glu Ser
    130                 135                 140
Arg Lys Lys Ile Asn Ser Trp Val Glu Ser Lys Thr Asn Glu Lys Ile
145                 150                 155                 160
Lys Asp Leu Phe Pro Asp Gly Ser Ile Ser Ser Ser Thr Lys Leu Val
                165                 170                 175
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```
Leu Val Asn Met Val Tyr Phe Lys Gly Gln Trp Asp Arg Glu Phe Lys
            180                 185                 190
Lys Glu Asn Thr Lys Glu Glu Lys Phe Trp Met Asn Lys Ser Thr Ser
        195                 200                 205
Lys Ser Val Gln Met Met Thr Gln Ser His Ser Phe Ser Phe Thr Phe
    210                 215                 220
Leu Glu Asp Leu Gln Ala Lys Ile Leu Gly Ile Pro Tyr Lys Asn Asn
225                 230                 235                 240
Asp Leu Ser Met Phe Val Leu Leu Pro Asn Asp Ile Asp Gly Leu Glu
                245                 250                 255
Lys Ile Ile Asp Lys Ile Ser Pro Glu Lys Leu Val Glu Trp Thr Ser
            260                 265                 270
Pro Gly His Met Glu Glu Arg Lys Val Asn Leu His Leu Pro Arg Phe
        275                 280                 285
Glu Val Glu Asp Ser Tyr Asp Leu Glu Ala Val Leu Ala Ala Met Gly
    290                 295                 300
Met Gly Asp Ala Phe Ser Glu His Lys Ala Asp Tyr Ser Gly Met Ser
305                 310                 315                 320
Ser Gly Ser Gly Leu Tyr Ala Gln Lys Phe Leu His Ser Ser Phe Val
                325                 330                 335
Ala Val Thr Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Gly Ile Gly
            340                 345                 350
Phe Thr Val Thr Ser Ala Pro Gly His Glu Asn Val His Cys Asn His
        355                 360                 365
Pro Phe Leu Phe Phe Ile Arg His Asn Glu Ser Asn Ser Ile Leu Phe
    370                 375                 380
Phe Gly Arg Phe Ser Ser Pro
385                 390
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<210> 111
<211> 1419
<212> DNA
<213> Homo sapien

<400> 111

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ggcgccgtca gcactcgact tgggtttgat cttttcaaag agctgaagaa aacaaatgat     180
ggcaacatct tcttttcccc tgtgggcatc ttgactgcaa ttggcatggt cctcctgggg     240
acccgaggag ccaccgcttc ccagttggag gaggtgtttc actctgaaaa agagacgaag     300
agctcaagaa taaaggctga agaaaaagag gtggtaagaa taaaggctga aggaaaagag     360
attgagaaca cagaagcagt acatcaacaa ttccaaaagt ttttgactga aataagcaaa     420
ctcactaatg attatgaact gaacataacc aacaggctgt ttggagaaaa aacatacctc     480
ttccttcaaa aatacttaga ttatgttgaa aaatattatc atgcatctct ggaacctgtt     540
gattttgtaa atgcagccga tgaaagtcga aagaagatta attcctgggt tgaaagcaaa     600
acaaatgaaa aaatcaagga cttgttccca gatggctcta ttagtagctc taccaagctg     660
gtgctggtga acatggttta ttttaaaggg caatgggaca gggagtttaa gaaagaaaat     720
actaaggaag agaaatttg gatgaataag agcacaagta aatctgtaca gatgatgaca     780
cagagccatt cctttagctt cactttcctg gaggacttgc aggccaaaat tctagggatt     840
ccatataaaa acaacgacct aagcatgttt gtgcttctgc ccaacgacat cgatggcctg     900
gagaagataa tagataaaat aagtcctgag aaattggtag agtggactag tccagggcat     960
atggaagaaa gaaaggtgaa tctgcacttg ccccggtttg aggtggagga cagttacgat    1020
ctagaggcgg tcctggctgc catggggatg ggcgatgcct tcagtgagca caaagccgac    1080
tactcgggaa tgtcgtcagg ctccgggttg tacgcccaga agttcctgca cagttccttt    1140
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acatccgccc caggtcatga aaatgttcac tgcaatcatc ccttcctgtt cttcatcagg 1260
cacaatgaat ccaacagcat cctcttcttc ggcagatttt cttctcctta agatgatcgt 1320
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<210> 112
<211> 400
<212> PRT
<213> Homo sapien

<400> 112

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Lys Glu Leu Lys Lys Thr Asn Asp Gly Asn Ile Phe Phe Ser Pro Val
            20                  25                  30
Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala
        35                  40                  45
Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
    50                  55                  60
Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Val Arg Ile Lys Ala
65                  70                  75                  80
Glu Gly Lys Glu Ile Glu Asn Thr Glu Ala Val His Gln Gln Phe Gln
                85                  90                  95
Lys Phe Leu Thr Glu Ile Ser Lys Leu Thr Asn Asp Tyr Glu Leu Asn
            100                 105                 110
Ile Thr Asn Arg Leu Phe Gly Glu Lys Thr Tyr Leu Phe Leu Gln Lys
        115                 120                 125
Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr His Ala Ser Leu Glu Pro Val
    130                 135                 140
Asp Phe Val Asn Ala Ala Asp Glu Ser Arg Lys Lys Ile Asn Ser Trp
145                 150                 155                 160
Val Glu Ser Lys Thr Asn Glu Lys Ile Lys Asp Leu Phe Pro Asp Gly
                165                 170                 175
Ser Ile Ser Ser Ser Thr Lys Leu Val Leu Val Asn Met Val Tyr Phe
            180                 185                 190
Lys Gly Gln Trp Asp Arg Glu Phe Lys Lys Glu Asn Thr Lys Glu Glu
        195                 200                 205
Lys Phe Trp Met Asn Lys Ser Thr Ser Lys Ser Val Gln Met Met Thr
    210                 215                 220
Gln Ser His Ser Phe Ser Phe Thr Phe Leu Glu Asp Leu Gln Ala Lys
225                 230                 235                 240
Ile Leu Gly Ile Pro Tyr Lys Asn Asn Asp Leu Ser Met Phe Val Leu
                245                 250                 255
Leu Pro Asn Asp Ile Asp Gly Leu Glu Lys Ile Ile Asp Lys Ile Ser
            260                 265                 270
Pro Glu Lys Leu Val Glu Trp Thr Ser Pro Gly His Met Glu Glu Arg
        275                 280                 285
Lys Val Asn Leu His Leu Pro Arg Phe Glu Val Glu Asp Ser Tyr Asp
    290                 295                 300
Leu Glu Ala Val Leu Ala Ala Met Gly Met Gly Asp Ala Phe Ser Glu
305                 310                 315                 320
His Lys Ala Asp Tyr Ser Gly Met Ser Ser Gly Ser Gly Leu Tyr Ala
                325                 330                 335
```

```
Gln Lys Phe Leu His Ser Ser Phe Val Ala Val Thr Glu Glu Gly Thr
            340                 345                 350
Glu Ala Ala Ala Ala Thr Gly Ile Gly Phe Thr Val Thr Ser Ala Pro
        355                 360                 365
Gly His Glu Asn Val His Cys Asn His Pro Phe Leu Phe Phe Ile Arg
    370                 375                 380
His Asn Glu Ser Asn Ser Ile Leu Phe Phe Gly Arg Phe Ser Ser Pro
385                 390                 395                 400
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<210> 113
<211> 957
<212> DNA
<213> Homo sapien

<400> 113

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gaaacatgag ttcttaccag cagaagcaga cctttacccc accacctcag cttcaacagc     180
agcaggtgaa acaacccagc cagcctccac ctcaggaaat atttgttccc acaaccaagg     240
agccatgcca ctcaaaggtt ccacaacctg gaaacacaaa gattccagag ccaggctgta     300
ccaaggtccc tgagccaggc tgtaccaagg tccctgagcc aggttgtacc aaggtccctg     360
agccaggatg taccaaggtc cctgagccag gttgtaccaa ggtccctgag ccaggctaca     420
ccaaggtccc tgagccaggc agcatcaagg tccctgacca aggcttcatc aagtttcctg     480
agccaggtgc catcaaagtt cctgagcaag gatacaccaa agttcctgtg ccaggctaca     540
caaaggtacc agagccatgt ccttcaacgg tcactccagg cccagctcag cagaagacca     600
agcagaagta atttggtgca cagacaagcc cttgagaagc caaccaccag atgctggaca     660
ccctcttccc atctgtttct gtgtcttaat tgtctgtaga ccttgtaatc agtacattct     720
caccccaagc catagtctct ctcttatttg tatcctaaaa atacggtact ataaagcttt     780
tgttcacaca cactctgaag aatcctgtaa gcccctgaat taagcagaaa gtcttcatgg     840
cttttctggt cttcggctgc tcagggttca tctgaagatt cgaatgaaaa gaaatgcatg     900
tttcctgctc tgccctcatt aaattgcttt taattccaaa aaaaaaaaaa aaaaaaa        957
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<210> 114
<211> 161
<212> PRT
<213> Homo sapien

<400> 114

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Met Ser Ser Tyr Gln Gln Lys Gln Thr Phe Thr Pro Pro Pro Gln Leu
 1               5                  10                  15
Gln Gln Gln Gln Val Lys Gln Pro Ser Gln Pro Pro Pro Gln Glu Ile
            20                  25                  30
Phe Val Pro Thr Thr Lys Glu Pro Cys His Ser Lys Val Pro Gln Pro
        35                  40                  45
Gly Asn Thr Lys Ile Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
    50                  55                  60
Gly Cys Thr Lys Val Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
65                  70                  75                  80
Gly Cys Thr Lys Val Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
                85                  90                  95
Gly Tyr Thr Lys Val Pro Glu Pro Gly Ser Ile Lys Val Pro Asp Gln
            100                 105                 110
Gly Phe Ile Lys Phe Pro Glu Pro Gly Ala Ile Lys Val Pro Glu Gln
        115                 120                 125
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Gly Tyr Thr Lys Val Pro Val Pro Gly Tyr Thr Lys Val Pro Glu Pro
130 135 140
Cys Pro Ser Thr Val Thr Pro Gly Pro Ala Gln Gln Lys Thr Lys Gln
145 150 155 160
Lys

<210> 115
<211> 506
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(506)
<223> n = A,T,C or G

<400> 115
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angtanagat gttctggata ccattanatn tgccccngt gtcagaggct catattgtgt 180
tatgtaaatg gtatntcatt cgctactatn antcaattng aaatanggtc tttgggttat 240
gaatantnng cagcncanct nanangctgt ctgtngtatt cattgtggtc atagcacctc 300
acancattgt aacctcnatc nagtgagaca nactagnaan ttcctagtga tggctcanga 360
ttccaaatgg nctcatntcn aatgtttaaa agttanttaa gtgtaagaaa tacagactgg 420
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gactgtggta ncccgcatcg gaaaaa 506

<210> 116
<211> 3079
<212> DNA
<213> Homo sapien

<400> 116
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aaagaggtca aagtggttta taggggcgc tgagggcttc ccacattctc tggcctaaac 180
cttgcaggca gatctgccca gtgggctctg ggatagctgt gccttcccta acaaaaaaat 240
tgtgcacaaa aggatgaaac tctattttcc ctctagcaca taaccaagaa tataaggcta 300
cagattgcct ttcccagagg gaaaaccctg cagcaacctg ctgcctggaa aagtgtaaga 360
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<210> 117
<211> 6921
<212> DNA
<213> Homo sapien

<400> 117
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taaatggaag gtcattagtc ctactgggaa tgaggctatg gtcccatctg tgtgcttcac 180
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<211> 2294
<212> DNA
<213> Homo sapien

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<211> 956
<212> DNA
<213> Homo sapien

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<210> 125
<211> 486
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(486)
<223> n = A,T,C or G

<400> 125
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<210> 126
<211> 3552
<212> DNA
<213> Homo sapien

<400> 126
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<210> 127
<211> 754
<212> DNA
<213> Homo sapien

<400> 127
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<210> 128
<211> 374
<212> DNA
<213> Homo sapien

<400> 128
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<210> 129
<211> 546
<212> DNA
<213> Homo sapien

<400> 129
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<210> 130
<211> 5156
<212> DNA
<213> Homo sapien

<400> 130
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<212> DNA
<213> Homo sapien

<400> 135

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<210> 140
<211> 370
<212> DNA
<213> Homo sapien

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aatagaggta tttttaggct atttttgtaa tatggcttct ggtcaaaatc cctgtgtagc 240
tgaattccca agccctgcat tgtacagccc cccactcccc tcaccaccta ataaaggaat 300
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gcacactggc 370

<210> 141
<211> 371
<212> DNA
<213> Homo sapien

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aaggagcttc agggtcctgg tactcctcca cagaatactc ggagtattca gagtactcat 180
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catggagctg ggagccggca gtgtctgcag cataactagg gaggggtcgt gatccagatg 300
cgatgaactg gccctggcag gcacagtgct gactcatctc ttggcgacct gcccgggcgg 360
ccgctcgaag c 371

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<211> 343
<212> DNA
<213> Homo sapien

<400> 142
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agagcagttt tgaaacactc ttttgtagaa tttgcaagcg gatgattgga tcgctatgag 180
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tctttgggat gtgggcattc aacccacaga ggagaacttc atttgataga gcagttttga 300
aacacccttt ttgtagaatc tacaggtgga catttagagt gct 343

<210> 143
<211> 354
<212> DNA
<213> Homo sapien

<400> 143
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agcaaatctc catactgttt ctttcttttt tttttcatta ctgtgttcaa ttatctttat 300
cataaacatt ttacatgcag ctatttcaaa gtgtgttgga ttaattagga tcat 354

<210> 144
<211> 353
<212> DNA
<213> Homo sapien

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gttaagttgc ttaactttca ttctgtctta cgatagtctt cagaggtggg aacagatgaa 240
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<210> 145
<211> 371
<212> DNA
<213> Homo sapien

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tagtggatcc g 371

<210> 146
<211> 355
<212> DNA
<213> Homo sapien

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tggtcaggaa aaagactaca atgtactagt catggatctt ctgggaccta gcctc 355

<210> 147
<211> 355
<212> DNA
<213> Homo sapien

<400> 147
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<210> 148

<211> 369
<212> DNA
<213> Homo sapien

<400> 148
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agggagtgtg ccgagggctt ctgagaaggt ttctctcaca tctagaaaga agcgcttaag 180
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<210> 149
<211> 620
<212> DNA
<213> Homo sapien

<220>
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<222> (1)...(620)
<223> n = A,T,C or G

<400> 149
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<210> 150
<211> 371
<212> DNA
<213> Homo sapien

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<210> 151
<211> 4655
<212> DNA
<213> Homo sapien

<400> 151

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<210> 152
<211> 586
<212> PRT
<213> Homo sapien

<400> 152

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Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
        35                  40                  45
Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
    50                  55                  60
Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
65                  70                  75                  80
His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
                85                  90                  95
Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
            100                 105                 110
Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
        115                 120                 125
Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
    130                 135                 140
Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
145                 150                 155                 160
Glu Gly Gln Ile Ala Pro Ser Ser His Leu Ile Arg Val Glu Gly Asn
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Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
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Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val
225                 230                 235                 240
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Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
            260                 265                 270
Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr
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His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp
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Glu Leu Val Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu
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Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu
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Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser
        355                 360                 365
Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val
    370                 375                 380
Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr
385                 390                 395                 400
Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met
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Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro
            420                 425                 430
Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro
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Tyr Pro Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys
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Ser Ser Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr
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Gln Ile Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro
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Glu Gln Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln
            500                 505                 510
Leu His Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser
        515                 520                 525
Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val
    530                 535                 540
Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro
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<211> 2007
<212> DNA
<213> Homo sapien

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tggcttagca ttttctacat catattgtaa tcgtcttatt tgctagtttt cttccttact 1920
gtgagtgact aacagtcatc tttatcccag tgcctggtac ataataagtg atcaataaat 1980
gttgattgac taaaaaaaaa aaaaaaa 2007

<210> 154
<211> 2148
<212> DNA
<213> Homo sapien

<400> 154
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tggccagggc aattttggag agcaaaaaat ttgcagtgag agcagtgacc agggatgtga 180
cttgaccaaa tgccctggag ctccagcgcc ttggagctga ggtggtcaaa ggtgacctga 240
atgataaagc atcggtggac agtgccttaa aaggggaagc tggtggcaga ctccgccaag 300
cacctgggtc tgaagcacgt ggtgtacagc ggcctggaga acgtcaagcg actgacggat 360
ggcaagctgg aggtgccgca ctttgacagc aagggcgagg tggaggagta cttctggtcc 420

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attggcatcc ccatgaccag tgtccgcgtg gcggcctact ttgaaaactt tctcgcggcg     480
tggcggcccg tgaaagcctc tgatggagat tactacacct tggctgtacc gatgggagat     540
gtaccaatgg atggtatctc tgttgctgat attggagcag ccgtctctag cattttaat      600
tctccagagg aatttttagg caaggccgtg gggctcagtg cagaagcact aacaatacag     660
caatatgctg atgttttgtc caaggctttg gggaaagaag tccgagatgc aaagactatc     720
tgtgctatag atgaccagaa aacagtggaa gaaggtttca tggaagacgt gggcttgagt     780
tggtccttga gggaacatga ccatgtatag acagaggagg catcaagaag gctggcctgg     840
ctaattctgg aataaacacg acaaaccaga ggcagtacgg gaaggaggca aattctggct     900
ctgcctctat ccttgattac cccggaagct ttcgagaagc tgggattccc tgcagcaaag     960
gaaatagcca atatgtgtcg tttctatgaa atgaagccag accgagatgt caatctcacc    1020
caccaactaa atcccaaagt caaaagcttc agccatttta tctcagagaa ccagggagcc    1080
ttcaagggca tgtagaaaat cagctgttca gataggcctc tgcaccacac agcctctttc    1140
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caattgtttg caacaccgaa ggatttcctg cggtcgcctc ttcagtagga agcactgcat    1260
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acaactgttt ggtaaaatga gaagcctcgg aacttggagc ttctctccta ccactaatgg    1380
gagggcagat tatactggga tttctcctgg gtgagtaatt tcaagcccta atgctgaaat    1440
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atgaacaagc acaagcattg gaaatgctaa aattcagttt tgcctcaaga ttggaagttt    1620
attttctgac tcattcatga agtcatctat tgagccacca ttcaattatt catctattaa    1680
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atttgtggac ttctcttcat tcctatgtgt tttcttatca aagtgatcca ctctcgaaag    1800
gctcctttcc agtctgtggt tgggttcaag tcatgccagg gccagggggc ccatctcctc    1860
gtttagctct aggcaaaatc caggggatct gcagtgggga gcgggggcag gaagctggag    1920
ggaaggcctg tgaagggtag ggatgtggaa agacaaggtg acagaaggac ccaataggac    1980
ctttctatat ctctggctta gcattttcta catcatattg taatcgtctt atttgctagt    2040
tttcttcctt actgtgagtg actaacagtc atctttatcc cagtgcctgg tacataataa    2100
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<210> 155
<211> 153
<212> PRT
<213> Homo sapien

<400> 155

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Met Thr Ser Val Arg Val Ala Ala Tyr Phe Glu Asn Phe Leu Ala Ala
 1               5                  10                  15
Trp Arg Pro Val Lys Ala Ser Asp Gly Asp Tyr Tyr Thr Leu Ala Val
            20                  25                  30
Pro Met Gly Asp Val Pro Met Asp Gly Ile Ser Val Ala Asp Ile Gly
        35                  40                  45
Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys
    50                  55                  60
Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp
65                  70                  75                  80
Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Ile Thr
                85                  90                  95
Pro Glu Ala Phe Glu Lys Leu Gly Phe Pro Ala Ala Lys Glu Ile Ala
            100                 105                 110
Asn Met Cys Arg Phe Tyr Glu Met Lys Pro Asp Arg Asp Val Asn Leu
        115                 120                 125
Thr His Gln Leu Asn Pro Lys Val Lys Ser Phe Ser Gln Phe Ile Ser
    130                 135                 140
```

Glu Asn Gln Gly Ala Phe Lys Gly Met
145 150

<210> 156
<211> 128
<212> PRT
<213> Homo sapien

<400> 156
Met Thr Ser Val Arg Val Ala Ala Tyr Phe Glu Asn Phe Leu Ala Ala
1 5 10 15
Trp Arg Pro Val Lys Ala Ser Asp Gly Asp Tyr Tyr Thr Leu Ala Val
20 25 30
Pro Met Gly Asp Val Pro Met Asp Gly Ile Ser Val Ala Asp Ile Gly
35 40 45
Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys
50 55 60
Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp
65 70 75 80
Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Thr Ile
85 90 95
Cys Ala Ile Asp Asp Gln Lys Thr Val Glu Glu Gly Phe Met Glu Asp
100 105 110
Val Gly Leu Ser Trp Ser Leu Arg Glu His Asp His Val Ala Gly Ala
115 120 125

<210> 157
<211> 424
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(424)
<223> n = A,T,C or G

<400> 157
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ggatacatta cagcagacat ggaaatataa ttttaaaaaa tttctctcca acctccttca 120
aattcagtca ccactgttat attaccttct ccaggaaccc tccagtgggg aaggctgcga 180
tattagattt ccttgtatgc aaagtttttg ttgaaagctg tgctcagagg aggtgagagg 240
agaggaagga gaaaactgca tcataacttt acagaattga atctagagtc ttccccgaaa 300
agcccagaaa cttctctgcn gnatctggct tgtccatctg gtctaaggtg gctgcttctt 360
ccccagccat cgagtcagtt tgtgcccatg aataatacac gacctgctat ttcccatgac 420
tgct 424

<210> 158
<211> 2099
<212> DNA
<213> Homo sapien

<400> 158
ccgcggttaa aaggcgcagc aggtgggagc cggggccttc acccgaaacc cgacgagagc 60
ccgacagccg gcggcgcccg agcccgacct gcctgcccag ccggagcgaa gggcgccgcc 120

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ccgcgcagag cccgcgccag ggccgccggc cgcagagcag ttaaaacgtg caggcaccag     180
aaggcacttc ctgtcggtga agaagacctg tctccggtgt cacgggcatc ctgtgttttg     240
caaacggggc tgacctccct tcctggggag caggaagggt cagggaagga aaagaagtac     300
agaagatctg gctaaacaat ttctgtatgg cgaaagaaaa attctaactt gtacgccctc     360
ttcatgcatc tttaattcaa tttgaatatt ccaggcgaca tcctcactga ccgagcaaag     420
attgacattc gtatcatcac tgtgcaccat tggcttctag gcactccagt ggggtaggag     480
aaggaggtct gaaaccctcg cagagggatc ttgccctcat tctttgggtc tgaaacactg     540
gcagtcgttg gaaacaggac tcagggataa accagcgcaa tggattgggg gacgctgcac     600
actttcatcg ggggtgtcaa caaacactcc accagcatcg ggaaggtgtg gatcacagtc     660
atctttattt tccgagtcat gatcctcgtg gtggctgccc aggaagtgtg gggtgacgag     720
caagaggact tcgtctgcaa cacactgcaa ccgggatgca aaaatgtgtg ctatgaccac     780
tttttcccgg tgtcccacat ccggctgtgg gccctccagc tgatcttcgt ctccacccca     840
gcgctgctgg tggccatgca tgtggcctac tacaggcacg aaaccactcg caagttcagg     900
cgaggagaga agaggaatga tttcaaagac atagaggaca ttaaaaagca gaaggttcgg     960
atagaggggt cgctgtggtg gacgtacacc agcagcatct ttttccgaat catctttgaa    1020
gcagccttta tgtatgtgtt ttacttcctt tacaatgggt accacctgcc ctgggtgttg    1080
aaatgtggga ttgacccctg ccccaacctt gttgactgct ttatttctag gccaacagag    1140
aagaccgtgt ttaccatttt tatgatttct gcgtctgtga tttgcatgct gcttaacgtg    1200
gcagagttgt gctacctgct gctgaaagtg tgttttagga gatcaaagag agcacagacg    1260
caaaaaaatc accccaatca tgccctaaag gagagtaagc agaatgaaat gaatgagctg    1320
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tgtagctgcg tcataaggag acttctgtct tctccagaag gcaataccaa cctgaaagtt    1440
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atttatccag gaattgatac gtttattagg aaaagatatt tttataggct tggatgtttt    1740
tagttctgac tttgaattta tataaagtat ttttataatg actggtcttc cttacctgga    1800
aaaacatgcg atgttagttt tagaattaca ccacaagtat ctaaatttgg aacttacaaa    1860
gggtctatct tgtaaatatt gttttgcatt gtctgttggc aaatttgtga actgtcatga    1920
tacgcttaag gtggaaagtg ttcattgcac aatatatttt tactgctttc tgaatgtaga    1980
cggaacagtg tggaagcaga aggctttttt aactcatccg tttgccaatc attgcaaaca    2040
actgaaatgt ggatgtgatt gcctcaataa agctcgtccc cattgcttaa aaaaaaaaa     2099
```

<210> 159
<211> 291
<212> PRT
<213> Homo sapien

<400> 159

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Met Asp Trp Gly Thr Leu His Thr Phe Ile Gly Gly Val Asn Lys His
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Ser Thr Ser Ile Gly Lys Val Trp Ile Thr Val Ile Phe Ile Phe Arg
            20                  25                  30
Val Met Ile Leu Val Val Ala Ala Gln Glu Val Trp Gly Asp Glu Gln
        35                  40                  45
Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
    50                  55                  60
Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln
65                  70                  75                  80
Leu Ile Phe Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala
                85                  90                  95
Tyr Tyr Arg His Glu Thr Thr Arg Lys Phe Arg Arg Gly Glu Lys Arg
            100                 105                 110
```

```
Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys Gln Lys Val Arg Ile
        115                 120                 125
Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Ile
    130                 135                 140
Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Phe Leu Tyr Asn Gly
145                 150                 155                 160
Tyr His Leu Pro Trp Val Leu Lys Cys Gly Ile Asp Pro Cys Pro Asn
                165                 170                 175
Leu Val Asp Cys Phe Ile Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
            180                 185                 190
Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala
        195                 200                 205
Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys Phe Arg Arg Ser Lys Arg
    210                 215                 220
Ala Gln Thr Gln Lys Asn His Pro Asn His Ala Leu Lys Glu Ser Lys
225                 230                 235                 240
Gln Asn Glu Met Asn Glu Leu Ile Ser Asp Ser Gly Gln Asn Ala Ile
                245                 250                 255
Thr Gly Ser Gln Ala Lys His Phe Lys Val Lys Cys Ser Cys Val Ile
            260                 265                 270
Arg Arg Leu Leu Ser Ser Pro Glu Gly Asn Thr Asn Leu Lys Val Pro
        275                 280                 285
Ser Val Ala
    290
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<210> 160
<211> 3951
<212> DNA
<213> Homo sapien

<400> 160

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tgtgactctc ctggttgcct taagttcaga actcccattc ctgggagctg gagtacagct     180
tcaagacaat gggtataatg gattgctcat tgcaattaat cctcaggtac ctgagaatca     240
gaacctcatc tcaaacatta aggaaatgat aactgaagct tcattttacc tatttaatgc     300
taccaagaga agagtatttt tcagaaatat aaagatttta atacctgcca catggaaagc     360
taataataac agcaaaataa aacaagaatc atatgaaaag gcaaatgtca tagtgactga     420
ctggtatggg gcacatggag atgatccata caccctacaa tacagagggt gtggaaaaga     480
gggaaaatac attcatttca cacctaattt cctactgaat gataacttaa cagctggcta     540
cggatcacga ggccgagtgt ttgtccatga atgggcccac ctccgttggg gtgtgttcga     600
tgagtataac aatgacaaac ctttctacat aaatgggcaa aatcaaatta aagtgacaag     660
gtgttcatct gacatcacag gcatttttgt gtgtgaaaaa ggtccttgcc cccaagaaaa     720
ctgtattatt agtaagcttt ttaaagaagg atgcaccttt atctacaata gcacccaaaa     780
tgcaactgca tcaataatgt tcatgcaaag tttatcttct gtggttgaat tttgtaatgc     840
aagtacccac aaccaagaag caccaaacct acagaaccag atgtgcagcc tcagaagtgc     900
atgggatgta atcacagact ctgctgactt tcaccacagc tttcccatga acgggactga     960
gcttccacct cctcccacat tctcgcttgt agaggctggt gacaaagtgg tctgtttagt    1020
gctggatgtg tccagcaaga tggcagaggc tgacagactc cttcaactac aacaagccgc    1080
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cagcaaagga gagatcagag cccagctaca ccaaattaac agcaatgatg atcgaaagtt    1200
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gcttaagaaa ggatttgagg tggttgaaaa actgaatgga aaagcttatg gctctgtgat    1320
gatattagtg accagcggag atgataagct tcttggcaat tgcttaccca ctgtgctcag    1380
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catgattgat gctttcagta gaatttcctc tggaactgga gacattttcc agcaacatat 1560
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tgtggataat actgtgggca acgacactat gtttctagtt acgtggcagg ccagtggtcc 1680
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gacttacacc ctgaacaata cccatcattc tctgcaagcc ctgaaagtga cagtgacctc 1860
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cctccatttt cctcatcctg tgatgattta tgccaatgtg aaacagggat tttatcccat 1980
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atgggtatta cctttgtctc ttcataccgg ttttatgaca aaggtctatt gaatttattt 3540
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gattatcgaa caataaaatc atttgccttt ttaattaaaa acataaaaaa a 3951

<210> 161
<211> 943
<212> PRT
<213> Homo sapien

<400> 161

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Met Thr Gln Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val
 1               5                  10                  15
Thr Leu Leu Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly
            20                  25                  30
```

```
Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
        35                  40                  45
Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
    50                  55                  60
Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
65                  70                  75                  80
Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
                85                  90                  95
Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
            100                 105                 110
Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
        115                 120                 125
Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
    130                 135                 140
Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
145                 150                 155                 160
Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
                165                 170                 175
Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
            180                 185                 190
Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
        195                 200                 205
Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
    210                 215                 220
Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
225                 230                 235                 240
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
                245                 250                 255
Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
            260                 265                 270
Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser
        275                 280                 285
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu
    290                 295                 300
Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser
305                 310                 315                 320
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu
                325                 330                 335
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala
            340                 345                 350
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn
        355                 360                 365
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val
    370                 375                 380
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe
385                 390                 395                 400
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile
                405                 410                 415
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr
            420                 425                 430
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser
        435                 440                 445
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys
    450                 455                 460
```

```
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe
465                 470                 475                 480
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
                485                 490                 495
Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
            500                 505                 510
Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
        515                 520                 525
Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
    530                 535                 540
Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
545                 550                 555                 560
Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
                565                 570                 575
Tyr Thr Leu Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr
            580                 585                 590
Val Thr Ser Arg Ala Ser Asn Ser Ala Val Pro Pro Ala Thr Val Glu
        595                 600                 605
Ala Phe Val Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile
    610                 615                 620
Tyr Ala Asn Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val
625                 630                 635                 640
Thr Ala Thr Val Glu Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu
                645                 650                 655
Leu Asp Asp Gly Ala Gly Ala Asp Val Ile Lys Asn Asp Gly Ile Tyr
            660                 665                 670
Ser Arg Tyr Phe Phe Ser Phe Ala Ala Asn Gly Arg Tyr Ser Leu Lys
        675                 680                 685
Val His Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile
    690                 695                 700
Pro Gly Ser His Ala Met Tyr Val Pro Gly Tyr Thr Ala Asn Gly Asn
705                 710                 715                 720
Ile Gln Met Asn Ala Pro Arg Lys Ser Val Gly Arg Asn Glu Glu Glu
                725                 730                 735
Arg Lys Trp Gly Phe Ser Arg Val Ser Ser Gly Gly Ser Phe Ser Val
            740                 745                 750
Leu Gly Val Pro Ala Gly Pro His Pro Asp Val Phe Pro Pro Cys Lys
        755                 760                 765
Ile Ile Asp Leu Glu Ala Val Lys Val Glu Glu Glu Leu Thr Leu Ser
    770                 775                 780
Trp Thr Ala Pro Gly Glu Asp Phe Asp Gln Gly Gln Ala Thr Ser Tyr
785                 790                 795                 800
Glu Ile Arg Met Ser Lys Ser Leu Gln Asn Ile Gln Asp Asp Phe Asn
                805                 810                 815
Asn Ala Ile Leu Val Asn Thr Ser Lys Arg Asn Pro Gln Gln Ala Gly
            820                 825                 830
Ile Arg Glu Ile Phe Thr Phe Ser Pro Gln Ile Ser Thr Asn Gly Pro
        835                 840                 845
Glu His Gln Pro Asn Gly Glu Thr His Glu Ser His Arg Ile Tyr Val
    850                 855                 860
Ala Ile Arg Ala Met Asp Arg Asn Ser Leu Gln Ser Ala Val Ser Asn
865                 870                 875                 880
Ile Ala Gln Ala Pro Leu Phe Ile Pro Pro Asn Ser Asp Pro Val Pro
                885                 890                 895
```

```
Ala Arg Asp Tyr Leu Ile Leu Lys Gly Val Leu Thr Ala Met Gly Leu
            900                 905                 910
Ile Gly Ile Ile Cys Leu Ile Ile Val Val Thr His His Thr Leu Ser
        915                 920                 925
Arg Lys Lys Arg Ala Asp Lys Lys Glu Asn Gly Thr Lys Leu Leu
    930                 935                 940
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<210> 162
<211> 498
<212> DNA
<213> Homo sapien

<400> 162

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tggagaacca cgtggacagc accatgaaca tgttgggcgg gggaggcagt gctggccgga      60
agcccctcaa gtcgggtatg aaggagctgg ccgtgttccg ggagaaggtc actgagcagc     120
accggcagat gggcaagggt ggcaagcatc accttggcct ggaggagccc aagaagctgc     180
gaccaccccc tgccaggact ccctgccaac aggaactgga ccaggtcctg gagcggatct     240
ccaccatgcg ccttccggat gagcggggcc ctctggagca cctctactcc ctgcacatcc     300
ccaactgtga caagcatggc ctgtacaacc tcaaacagtg gcaagatgtc tctgaacggg     360
cagcgtgggg agtgctggtg tgtgaacccc aacaccggga agctgatcca gggagccccc     420
accatccggg gggaccccga gtgtcatctc ttctacaatg agcagcagga ggctcgcggg     480
gtgcacaccc cagcggat                                                   498
```

<210> 163
<211> 1128
<212> DNA
<213> Homo sapien

<400> 163

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gccacctggc cctcctgatc gacgacacac gcacttgaaa cttgttctca gggtgtgtgg      60
aatcaacttt ccggaagcaa ccagcccacc agaggaggtc ccgagcgcga gcggagacga     120
tgcagcggag actggttcag cagtggagcg tcgcggtgtt cctgctgagc tacgcggtgc     180
cctcctgcgg gcgctcggtg gagggtctca gccgccgcct caaaagagct gtgtctgaac     240
atcagctcct ccatgacaag gggaagtcca tccaagattt acggcgacga ttcttccttc     300
accatctgat cgcagaaatc cacacagctg aaatcagagc tacctcggag gtgtccccta     360
actccaagcc ctctcccaac acaaagaacc accccgtccg atttgggtct gatgatgagg     420
gcagatacct aactcaggaa actaacaagg tggagacgta caaagagcag ccgctcaaga     480
cacctgggaa gaaaaagaaa ggcaagcccg ggaaacgcaa ggagcaggaa aagaaaaaac     540
ggcgaactcg ctctgcctgg ttagactctg gagtgactgg gagtgggcta gaaggggacc     600
acctgtctga cacctccaca acgtcgctgg agctcgattc acggaggcat tgaaattttc     660
agcagagacc ttccaaggac atattgcagg attctgtaat agtgaacata tggaaagtat     720
tagaaatatt tattgtctgt aaatactgta aatgcattgg aataaaactg tctcccccat     780
tgctctatga aactgcacat tggtcattgt gaatattttt ttttttgcca aggctaatcc     840
aattattatt atcacattta ccataattta ttttgtccat tgatgtattt attttgtaaa     900
tgtatcttgg tgctgctgaa tttctatatt ttttgtaaca taatgcactt tagatataca     960
tatcaagtat gttgataaat gacacaatga agtgtctcta ttttgtggtt gattttaatg    1020
aatgcctaaa tataattatc caaattgatt ttcctttgtg catgtaaaaa taacagtatt    1080
ttaaatttgt aaagaatgtc taataaaata taatctaatt acatcatg                 1128
```

<210> 164
<211> 1310
<212> DNA
<213> Homo sapien

<400> 164

gggcctggtt cgcaaagaag ctgacttcag aggggaaac tttcttcttt taggaggcgg 60
ttagccctgt tccacgaacc caggagaact gctggccaga ttaattagac attgctatgg 120
gagacgtgta aacacactac ttatcattga tgcatatata aaaccatttt attttcgcta 180
ttatttcaga ggaagcgcct ctgatttgtt tctttttttcc ctttttgctc tttctggctg 240
tgtggtttgg agaaagcaca gttggagtag ccggttgcta aataagtccc gagcgcgagc 300
ggagacgatg cagcggagac tggttcagca gtggagcgtc gcggtgttcc tgctgagcta 360
cgcggtgccc tcctgcgggc gctcggtgga gggtctcagc cgccgcctca aaagagctgt 420
gtctgaacat cagctcctcc atgacaaggg gaagtccatc caagatttac ggcgacgatt 480
cttccttcac catctgatcg cagaaatcca cacagctgaa atcagagcta cctcggaggt 540
gtcccctaac tccaagccct ctcccaacac aaagaaccac cccgtccgat ttgggtctga 600
tgatgagggc agatacctaa ctcaggaaac taacaaggtg gagacgtaca aagagcagcc 660
gctcaagaca cctgggaaga aaaagaaagg caagcccggg aaacgcaagg agcaggaaaa 720
gaaaaaacgg cgaactcgct ctgcctggtt agactctgga gtgactggga gtgggctaga 780
aggggaccac ctgtctgaca cctccacaac gtcgctggag ctcgattcac ggaggcattg 840
aaattttcag cagagacctt ccaaggacat attgcaggat tctgtaatag tgaacatatg 900
gaaagtatta gaaatattta ttgtctgtaa atactgtaaa tgcattggaa taaaactgtc 960
tcccccattg ctctatgaaa ctgcacattg gtcattgtga atatttttt ttttgccaag 1020
gctaatccaa ttattattat cacatttacc ataatttatt ttgtccattg atgtatttat 1080
tttgtaaatg tatcttggtg ctgctgaatt tctatatttt ttgtaacata atgcacttta 1140
gatatacata tcaagtatgt tgataaatga cacaatgaag tgtctctatt ttgtggttga 1200
ttttaatgaa tgcctaaata taattatcca aattgatttt cctttgtgcc cgtaaaaata 1260
acagtatttt aaatttgtaa agaatgtcta ataaaatata atctaattac 1310

<210> 165
<211> 177
<212> PRT
<213> Homo sapien

<400> 165

Met Gln Arg Arg Leu Val Gln Gln Trp Ser Val Ala Val Phe Leu Leu
1 5 10 15
Ser Tyr Ala Val Pro Ser Cys Gly Arg Ser Val Glu Gly Leu Ser Arg
20 25 30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
35 40 45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
50 55 60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65 70 75 80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
85 90 95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
100 105 110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Lys Gly
115 120 125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
130 135 140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145 150 155 160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg Arg
165 170 175
His

<210> 166
<211> 177
<212> PRT
<213> Homo sapien

<400> 166

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Met Gln Arg Arg Leu Val Gln Gln Trp Ser Val Ala Val Phe Leu Leu
 1               5                  10                  15
Ser Tyr Ala Val Pro Ser Cys Gly Arg Ser Val Glu Gly Leu Ser Arg
            20                  25                  30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
        35                  40                  45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
    50                  55                  60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65                  70                  75                  80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
                85                  90                  95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
            100                 105                 110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Lys Gly
        115                 120                 125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
    130                 135                 140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145                 150                 155                 160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg Arg
                165                 170                 175
His
```

<210> 167
<211> 3362
<212> DNA
<213> Homo sapien

<400> 167

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cacaatgtat gcagcaggct cagtgtgagt gaactggagg cttctctaca acatgaccca      60
aaggagcatt gcaggtccta tttgcaacct gaagtttgtg actctcctgg ttgccttaag     120
ttcagaactc ccattcctgg gagctggagt acagcttcaa gacaatgggt ataatggatt     180
gctcattgca attaatcctc aggtacctga gaatcagaac ctcatctcaa acattaagga     240
aatgataact gaagcttcat tttacctatt taatgctacc aagagaagag tatttttcag     300
aaatataaag attttaatac ctgccacatg gaaagctaat aataacagca aaataaaaca     360
agaatcatat gaaaaggcaa atgtcatagt gactgactgg tatggggcac atggagatga     420
tccatacacc ctacaataca gagggtgtgg aaaagaggga aaatacattc atttcacacc     480
taatttccta ctgaatgata acttaacagc tggctacgga tcacgaggcc gagtgtttgt     540
ccatgaatgg gcccacctcc gttggggtgt gttcgatgag tataacaatg acaaaccttt     600
ctacataaat gggcaaaatc aaattaaagt gacaaggtgt tcatctgaca tcacaggcat     660
ttttgtgtgt gaaaaaggtc cttgccccca agaaaactgt attattagta agctttttaa     720
agaaggatgc acctttatct acaatagcac ccaaaatgca actgcatcaa taatgttcat     780
gcaaagttta tcttctgtgg ttgaattttg taatgcaagt acccacaacc aagaagcacc     840
aaacctacag aaccagatgt gcagcctcag aagtgcatgg gatgtaatca cagactctgc     900
tgactttcac cacagctttc ccatgaacgg gactgagctt ccacctcctc ccacattctc     960
```

gcttgtagag gctggtgaca aagtggtctg tttagtgctg gatgtgtcca gcaagatggc 1020
agaggctgac agactccttc aactacaaca agccgcagaa ttttatttga tgcagattgt 1080
tgaaattcat accttcgtgg gcattgccag tttcgacagc aaaggagaga tcagagccca 1140
gctacaccaa attaacagca atgatgatcg aaagttgctg gtttcatatc tgcccaccac 1200
tgtatcagct aaaacagaca tcagcatttg ttcagggctt aagaaaggat ttgaggtggt 1260
tgaaaaactg aatggaaaag cttatggctc tgtgatgata ttagtgacca gcggagatga 1320
taagcttctt ggcaattgct tacccactgt gctcagcagt ggttcaacaa ttcactccat 1380
tgccctgggt tcatctgcag ccccaaatct ggaggaatta tcacgtctta caggaggttt 1440
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ttcctctgga actggagaca ttttccagca acatattcag cttgaaagta caggtgaaaa 1560
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cactatgttt ctagttacgt ggcaggccag tggtcctcct gagattatat tatttgatcc 1680
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ccatgcaaaa ttattgacct ggaagctgta aaagtagaag aggaattgac cctatcttgg 1860
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cgaaatcctc agcaagctgg catcagggag atatttacgt tctcacccca aatttccacg 2040
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actaacaaag tcaaattaac atcaaaactg tattaaaatg cattgagttt ttgtacaata 2460
cagataagat ttttacatgg tagatcaaca aattcttttt gggggtagat tagaaaaccc 2520
ttacactttg gctatgaaca aataataaaa attattcttt aaagtaatgt ctttaaaggc 2580
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tttcactgta agaggtaacc tttaacaata tgggtattac ctttgtctct tcataccggt 2940
tttatgacaa aggtctattg aatttatttg tttgtaagtt tctactccca tcaaagcagc 3000
tttctaagtt attgccttgg ttattatgga tgatagttat agcccttata atgccttaac 3060
taaggaagaa aagatgttat tctgagtttg ttttaataca tatatgaaca tatagtttta 3120
ttcaattaaa ccaaagaaga ggtcagcagg gagatactaa cctttggaaa tgattagctg 3180
gctctgtttt ttggttaaat aagagtcttt aatccttttct ccatcaagag ttacttacca 3240
agggcagggg aaggggggata tagaggtcac aaggaaataa aaatcatctt tcatctttaa 3300
ttttactcct tcctcttatt tttttaaaag attatcgaac aataaaatca tttgcctttt 3360
tt 3362

<210> 168
<211> 2784
<212> DNA
<213> Homo sapien

<400> 168
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gaggcttctc tacaacatga cccaaaggag cattgcaggt cctatttgca acctgaagtt 120
tgtgactctc ctggttgcct taagttcaga actcccattc ctgggagctg gagtacagct 180
tcaagacaat gggtataatg gattgctcat tgcaattaat cctcaggtac ctgagaatca 240
gaacctcatc tcaaacatta aggaaatgat aactgaagct tcatttacc tatttaatgc 300
taccaagaga agagtatttt tcagaaatat aaagatttta atacctgcca catggaaagc 360

```
taataataac agcaaaataa aacaagaatc atatgaaaag gcaaatgtca tagtgactga     420
ctggtatggg gcacatggag atgatccata caccctacaa tacagagggt gtggaaaaga     480
gggaaaatac attcatttca cacctaattt cctactgaat gataacttaa cagctggcta     540
cggatcacga ggccgagtgt ttgtccatga atgggcccac ctccgttggg gtgtgttcga     600
tgagtataac aatgacaaac ctttctacat aaatgggcaa aatcaaatta aagtgacaag     660
gtgttcatct gacatcacag gcatttttgt gtgtgaaaaa ggtccttgcc cccaagaaaa     720
ctgtattatt agtaagcttt ttaaagaagg atgcaccttt atctacaata gcacccaaaa     780
tgcaactgca tcaataatgt tcatgcaaag tttatcttct gtggttgaat tttgtaatgc     840
aagtacccac aaccaagaag caccaaacct acagaaccag atgtgcagcc tcagaagtgc     900
atgggatgta atcacagact ctgctgactt tcaccacagc tttcccatga acgggactga     960
gcttccacct cctcccacat tctcgcttgt agaggctggt gacaaagtgg tctgtttagt    1020
gctggatgtg tccagcaaga tggcagaggc tgacagactc cttcaactac aacaagccgc    1080
agaattttat ttgatgcaga ttgttgaaat tcataccttc gtgggcattg ccagtttcga    1140
cagcaaagga gagatcagag cccagctaca ccaaattaac agcaatgatg atcgaaagtt    1200
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gcttaagaaa ggatttgagg tggttgaaaa actgaatgga aaagcttatg gctctgtgat    1320
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cagtggttca acaattcact ccattgccct gggttcatct gcagccccaa atctggagga    1440
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catgattgat gctttcagta gaatttcctc tggaactgga gacattttcc agcaacatat    1560
tcagcttgaa agtacaggtg aaaatgtcaa acctcaccat caattgaaaa acacagtgac    1620
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tcctgagatt atattatttg atcctgatgg acgaaaatac tacacaaata attttatcac    1740
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gacttacacc ctgaacaata cccatcattc tctgcaagcc ctgaaagtga cagtgacctc    1860
tcgcgcctcc aactcagctg tgcccccagc cactgtggaa gcctttgtgg aaagagacag    1920
cctccatttt cctcatcctg tgatgattta tgccaatgtg aaacagggat tttatcccat    1980
tcttaatgcc actgtcactg ccacagttga gccagagact ggagatcctg ttacgctgag    2040
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cagcataagc accccagccc actctattcc agggagtcat gctatgtatg taccaggtta    2220
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acaatgctat tttagtaaat acatcaaagc gaaatcctca gcaagctggc atcagggaga    2580
tatttacgtt ctcaccccaa atttccacga atggacctga acatcagcca aatggagaaa    2640
cacatgaaag ccacagaatt tatgttgcaa tacgagcaat ggataggaac tccttacagt    2700
ctgctgtatc taacattgcc caggcgcctc tgtttattcc ccccaattct gatcctgtac    2760
ctgccagaga ttatcttata ttga                                           2784
```

<210> 169
<211> 592
<212> PRT
<213> Homo sapien

<400> 169

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Met Thr Gln Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val
 1               5                  10                  15
Thr Leu Leu Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly
            20                  25                  30
Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
        35                  40                  45
```

```
Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
    50                  55                  60
Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
65                  70                  75                  80
Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
                85                  90                  95
Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
            100                 105                 110
Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
        115                 120                 125
Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
    130                 135                 140
Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
145                 150                 155                 160
Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
                165                 170                 175
Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
            180                 185                 190
Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
        195                 200                 205
Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
    210                 215                 220
Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
225                 230                 235                 240
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
                245                 250                 255
Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
            260                 265                 270
Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser
        275                 280                 285
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu
    290                 295                 300
Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser
305                 310                 315                 320
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu
                325                 330                 335
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala
            340                 345                 350
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn
        355                 360                 365
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val
    370                 375                 380
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe
385                 390                 395                 400
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile
                405                 410                 415
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr
            420                 425                 430
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser
        435                 440                 445
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys
    450                 455                 460
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe
465                 470                 475                 480
```

```
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
                485                 490                 495
Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
            500                 505                 510
Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
        515                 520                 525
Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
    530                 535                 540
Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
545                 550                 555                 560
Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
                565                 570                 575
Tyr Thr Leu Met Cys Phe His His Ala Lys Leu Leu Thr Trp Lys Leu
            580                 585                 590
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<210> 170
<211> 791
<212> PRT
<213> Homo sapien

<400> 170

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Met Thr Gln Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val
 1               5                  10                  15
Thr Leu Leu Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly
            20                  25                  30
Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
        35                  40                  45
Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
    50                  55                  60
Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
65                  70                  75                  80
Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
                85                  90                  95
Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
            100                 105                 110
Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
        115                 120                 125
Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
    130                 135                 140
Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
145                 150                 155                 160
Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
                165                 170                 175
Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
            180                 185                 190
Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
        195                 200                 205
Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
    210                 215                 220
Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
225                 230                 235                 240
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
                245                 250                 255
Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
```

```
            260                 265                 270
Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser
        275                 280                 285
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu
    290                 295                 300
Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser
305                 310                 315                 320
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu
                325                 330                 335
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala
            340                 345                 350
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn
        355                 360                 365
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val
    370                 375                 380
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe
385                 390                 395                 400
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile
                405                 410                 415
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr
            420                 425                 430
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser
        435                 440                 445
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys
    450                 455                 460
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe
465                 470                 475                 480
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
                485                 490                 495
Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
            500                 505                 510
Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
        515                 520                 525
Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
    530                 535                 540
Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
545                 550                 555                 560
Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
                565                 570                 575
Tyr Thr Leu Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr
            580                 585                 590
Val Thr Ser Arg Ala Ser Asn Ser Ala Val Pro Pro Ala Thr Val Glu
        595                 600                 605
Ala Phe Val Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile
    610                 615                 620
Tyr Ala Asn Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val
625                 630                 635                 640
Thr Ala Thr Val Glu Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu
                645                 650                 655
Leu Asp Asp Gly Ala Gly Ala Asp Val Ile Lys Asn Asp Gly Ile Tyr
            660                 665                 670
Ser Arg Tyr Phe Phe Ser Phe Ala Ala Asn Gly Arg Tyr Ser Leu Lys
        675                 680                 685
Val His Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile
```

```
    690                 695                 700
Pro Gly Ser His Ala Met Tyr Val Pro Gly Tyr Thr Ala Asn Gly Asn
705                 710                 715                 720
Ile Gln Met Asn Ala Pro Arg Lys Ser Val Gly Arg Asn Glu Glu Glu
                725                 730                 735
Arg Lys Trp Gly Phe Ser Arg Val Ser Ser Gly Gly Ser Phe Ser Val
            740                 745                 750
Leu Gly Val Pro Ala Gly Pro His Pro Asp Val Phe Pro Pro Cys Lys
        755                 760                 765
Ile Ile Asp Leu Glu Ala Val Asn Arg Arg Gly Ile Asp Pro Ile Leu
    770                 775                 780
Asp Ser Thr Trp Arg Arg Leu
785                 790
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<210> 171
<211> 1491
<212> DNA
<213> Homo sapien

<400> 171

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aagagtgctg caacccagcc ctagccaacg ccgcatgaga gggagtgtgc cgagggcttc     120
tgagaaggtt tctctcacat ctagaaagaa gcgcttaaga tgtggcagcc cctcttcttc     180
aagtggctct tgtcctgttg ccctgggagt tctcaaattg ctgcagcagc ctccacccag     240
cctgaggatg acatcaatac acagaggaag aagagtcagg aaaagatgag agaagttaca     300
gactctcctg ggcgaccccg agagcttacc attcctcaga cttcttcaca tggtgctaac     360
agatttgttc ctaaaagtaa agctctagag gccgtcaaat tggcaataga agccgggttc     420
caccatattg attctgcaca tgtttacaat aatgaggagc aggttggact ggccatccga     480
agcaagattg cagatggcag tgtgaagaga gaagacatat tctacacttc aaagctttgg     540
agcaattccc atcgaccaga gttggtccga ccagccttgg aaaggtcact gaaaaatctt     600
caattggact atgttgacct ctatcttatt cattttccag tgtctgtaaa gccaggtgag     660
gaagtgatcc caaaagatga aaatggaaaa atactatttg acacagtgga tctctgtgcc     720
acatgggagg ccatggagaa gtgtaaagat gcaggattgg ccaagtccat cggggtgtcc     780
aacttcaacc acaggctgct ggagatgatc ctcaacaagc cagggctcaa gtacaagcct     840
gtctgcaacc aggtggaatg tcatccttac ttcaaccaga gaaaactgct ggatttctgc     900
aagtcaaaag acattgttct ggttgcctat agtgctctgg gatcccatcg agaagaacca     960
tgggtggacc cgaactcccc ggtgctcttg gaggacccag tcctttgtgc cttggcaaaa    1020
aagcacaagc gaaccccagc cctgattgcc ctgcgctacc agctgcagcg tggggttgtg    1080
gtcctggcca agagctacaa tgagcagcgc atcagacaga acgtgcaggt gtttgaattc    1140
cagttgactt cagaggagat gaaagccata gatggcctaa acagaaatgt gcgatatttg    1200
acccttgata tttttgctgg ccccccctaat tatccatttt ctgatgaata ttaacatgga    1260
gggcattgca tgaggtctgc cagaaggccc tgcgtgtgga tggtgacaca gaggatggct    1320
ctatgctggt gactggacac atcgcctctg gttaaatctc tcctgcttgg cgacttcagt    1380
aagctacagc taagcccatc ggccggaaaa gaaagacaat aattttgttt ttcattttga    1440
aaaaattaaa tgctctctcc taaagattct tcacctaaaa aaaaaaaaaa a              1491
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<210> 172
<211> 364
<212> PRT
<213> Homo sapien

<400> 172

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Met Trp Gln Pro Leu Phe Phe Lys Trp Leu Leu Ser Cys Cys Pro Gly
 1               5                  10                  15
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Ser Ser Gln Ile Ala Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp Ile
            20                  25                  30
Asn Thr Gln Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val Thr Asp
        35                  40                  45
Ser Pro Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr Ser Ser His
    50                  55                  60
Gly Ala Asn Arg Phe Val Pro Lys Ser Lys Ala Leu Glu Ala Val Lys
65                  70                  75                  80
Leu Ala Ile Glu Ala Gly Phe His His Ile Asp Ser Ala His Val Tyr
                85                  90                  95
Asn Asn Glu Glu Gln Val Gly Leu Ala Ile Arg Ser Lys Ile Ala Asp
            100                 105                 110
Gly Ser Val Lys Arg Glu Asp Ile Phe Tyr Thr Ser Lys Leu Trp Ser
        115                 120                 125
Asn Ser His Arg Pro Glu Leu Val Arg Pro Ala Leu Glu Arg Ser Leu
    130                 135                 140
Lys Asn Leu Gln Leu Asp Tyr Val Asp Leu Tyr Leu Ile His Phe Pro
145                 150                 155                 160
Val Ser Val Lys Pro Gly Glu Glu Val Ile Pro Lys Asp Glu Asn Gly
                165                 170                 175
Lys Ile Leu Phe Asp Thr Val Asp Leu Cys Ala Thr Trp Glu Ala Met
            180                 185                 190
Glu Lys Cys Lys Asp Ala Gly Leu Ala Lys Ser Ile Gly Val Ser Asn
        195                 200                 205
Phe Asn His Arg Leu Leu Glu Met Ile Leu Asn Lys Pro Gly Leu Lys
    210                 215                 220
Tyr Lys Pro Val Cys Asn Gln Val Glu Cys His Pro Tyr Phe Asn Gln
225                 230                 235                 240
Arg Lys Leu Leu Asp Phe Cys Lys Ser Lys Asp Ile Val Leu Val Ala
                245                 250                 255
Tyr Ser Ala Leu Gly Ser His Arg Glu Glu Pro Trp Val Asp Pro Asn
            260                 265                 270
Ser Pro Val Leu Leu Glu Asp Pro Val Leu Cys Ala Leu Ala Lys Lys
        275                 280                 285
His Lys Arg Thr Pro Ala Leu Ile Ala Leu Arg Tyr Gln Leu Gln Arg
    290                 295                 300
Gly Val Val Val Leu Ala Lys Ser Tyr Asn Glu Gln Arg Ile Arg Gln
305                 310                 315                 320
Asn Val Gln Val Phe Glu Phe Gln Leu Thr Ser Glu Glu Met Lys Ala
                325                 330                 335
Ile Asp Gly Leu Asn Arg Asn Val Arg Tyr Leu Thr Leu Asp Ile Phe
            340                 345                 350
Ala Gly Pro Pro Asn Tyr Pro Phe Ser Asp Glu Tyr
        355                 360
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<210> 173
<211> 1988
<212> DNA
<213> Homo sapiens

<400> 173
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ccgcgccgcc cgtcaacatg atccgctgcg gcctggcctg cgagcgctgc cgctggatcc 180
tgcccctgct cctactcagc gccatcgcct tcgacatcat cgcgctggcc ggccgcggct 240
ggttgcagtc tagcgaccac ggccagacgt cctcgctgtg gtggaaatgc tcccaagagg 300
gcggcggcag cgggtcctac gaggagggct gtcagagcct catggagtac gcgtggggta 360
gagcagcggc tgccatgctc ttctgtggct tcatcatcct ggtgatctgt ttcatcctct 420
ccttcttcgc cctctgtgga ccccagatgc ttgtcttcct gagagtgatt ggaggtctcc 480
ttgccttggc tgctgtgttc cagatcatct ccctggtaat ttaccccgtg aagtacaccc 540
agaccttcac ccttcatgcc aaccctgctg tcacttacat ctataactgg gcctacggct 600
ttgggtgggc agccacgatt atcctgatcg gctgtgcctt cttcttctgc tgcctcccca 660
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ttgggaatga atgtgggaga aaatcgctgc tgctgagatg gactccagaa gaagaaactg 780
tttctccagg cgactttgaa cccatttttt ggcagtgttc atattattaa actagtcaaa 840
aatgctaaaa taatttggga gaaaatattt tttaagtagt gttatagttt catgtttatc 900
ttttattatg ttttgtgaag ttgtgtcttt tcactaatta cctatactat gccaatattt 960
ccttatatct atccataaca tttatactac atttgtaaga gaatatgcac gtgaaactta 1020
acactttata aggtaaaaat gaggtttcca agatttaata atctgatcaa gttcttgtta 1080
tttccaaata gaatggactt ggtctgttaa gggctaagga gaagaggaag ataaggttaa 1140
aagttgttaa tgaccaaaca ttctaaaaga aatgcaaaaa aaaagtttat tttcaagcct 1200
tcgaactatt taaggaaagc aaaatcattt cctaaatgca tatcatttgt gagaatttct 1260
cattaatatc ctgaatcatt catttcagct aaggcttcat gttgactcga tatgtcatct 1320
aggaaagtac tatttcatgg tccaaacctg ttgccatagt tggtaaggct ttcctttaag 1380
tgtgaaatat ttagatgaaa ttttctcttt taaagttctt tatagggtta gggtgtggga 1440
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aaagctaatt gtagttttca ttatgaagtt ttcccaataa accaggtatt ctaaaaaaaa 1980
aaaaaaaa                                                          1988
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<210> 174
<211> 238
<212> PRT
<213> Homo sapiens

<400> 174

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Gly Ala Ala Ser Pro Arg Pro Leu Arg Phe Cys Gly Gly Ala Arg Ala
                  5                  10                  15

Arg Arg Pro Leu Ser Ala Val Ala Arg Pro Ala Arg Ser Ser Asp Pro
             20                  25                  30

Leu Arg Ser Ala Pro Leu Gly Pro Ala Pro Pro Val Asn Met Ile Arg
         35                  40                  45

Cys Gly Leu Ala Cys Glu Arg Cys Arg Trp Ile Leu Pro Leu Leu Leu
     50                  55                  60

Leu Ser Ala Ile Ala Phe Asp Ile Ile Ala Leu Ala Gly Arg Gly Trp
 65                  70                  75                  80
```

```
Leu Gln Ser Ser Asp His Gly Gln Thr Ser Ser Leu Trp Trp Lys Cys
                 85                  90                  95

Ser Gln Glu Gly Gly Gly Ser Gly Ser Tyr Glu Glu Gly Cys Gln Ser
            100                 105                 110

Leu Met Glu Tyr Ala Trp Gly Arg Ala Ala Ala Ala Met Leu Phe Cys
        115                 120                 125

Gly Phe Ile Ile Leu Val Ile Cys Phe Ile Leu Ser Phe Phe Ala Leu
    130                 135                 140

Cys Gly Pro Gln Met Leu Val Phe Leu Arg Val Ile Gly Gly Leu Leu
145                 150                 155                 160

Ala Leu Ala Ala Val Phe Gln Ile Ile Ser Leu Val Ile Tyr Pro Val
                165                 170                 175

Lys Tyr Thr Gln Thr Phe Thr Leu His Ala Asn Pro Ala Val Thr Tyr
            180                 185                 190

Ile Tyr Asn Trp Ala Tyr Gly Phe Gly Trp Ala Ala Thr Ile Ile Leu
        195                 200                 205

Ile Gly Cys Ala Phe Phe Phe Cys Cys Leu Pro Asn Tyr Glu Asp Asp
    210                 215                 220

Leu Leu Gly Asn Ala Lys Pro Arg Tyr Phe Tyr Thr Ser Ala
225                 230                 235
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Sequence Listing

<210> 175
<211> 4181
<212> DNA
<213> Homo sapiens

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<400> 175
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ttactgtgtt tgtgtatttt aaaggcgaga agacgagggg aacaaaacca gctggatcca 180
tccatcaccg tgggtggttt taatttttcg ttttttctcg ttatttttt ttaaacaacc 240
actcttcaca atgaacaaac tgtatatcgg aaacctcagc gagaacgccg ccccctcgga 300
cctagaaagt atcttcaagg acgccaagat cccggtgtcg ggacccttcc tggtgaagac 360
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ttcaggtaaa atagaactgc acgggaaacc catagaagtt gagcactcgg tcccaaaaag 480
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caaactgaat ggatttcagt tagagaattt caccttgaaa gtagcctata tccctgatga 720
aatggccgcc cagcaaaacc ccttgcagca gccccgaggt cgccgggggc ttgggcagag 780
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cccgcagttt gagcaatcag aaacggagac tgttcatcag tttatcccag ctctatcagt 1500
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ttcaattaag attgctccag cggaagcacc agatgctaaa gtgaggatgg tgattatcac 1620
tggaccacca gaggctcagt tcaaggctca gggaagaatt tatggaaaaa ttaaagaaga 1680
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<210> 176
<211> 579
<212> PRT

<213> Homo sapiens

<400> 176

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Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
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Asp Leu Glu Ser Ile Phe Lys Asp Ala Lys Ile Pro Val Ser Gly Pro
             20                  25                  30

Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu Ser
         35                  40                  45

Trp Ala Leu Lys Ala Ile Glu Ala Leu Ser Gly Lys Ile Glu Leu His
     50                  55                  60

Gly Lys Pro Ile Glu Val Glu His Ser Val Pro Lys Arg Gln Arg Ile
 65                  70                  75                  80

Arg Lys Leu Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu Val
                 85                  90                  95

Leu Asp Ser Leu Leu Val Gln Tyr Gly Val Val Glu Ser Cys Glu Gln
            100                 105                 110

Val Asn Thr Asp Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Ser
        115                 120                 125

Lys Asp Gln Ala Arg Gln Ala Leu Asp Lys Leu Asn Gly Phe Gln Leu
    130                 135                 140

Glu Asn Phe Thr Leu Lys Val Ala Tyr Ile Pro Asp Glu Met Ala Ala
145                 150                 155                 160

Gln Gln Asn Pro Leu Gln Gln Pro Arg Gly Arg Arg Gly Leu Gly Gln
                165                 170                 175

Arg Gly Ser Ser Arg Gln Gly Ser Pro Gly Ser Val Ser Lys Gln Lys
            180                 185                 190

Pro Cys Asp Leu Pro Leu Arg Leu Leu Val Pro Thr Gln Phe Val Gly
        195                 200                 205

Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln
    210                 215                 220

Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala
225                 230                 235                 240

Glu Lys Ser Ile Thr Ile Leu Ser Thr Pro Glu Gly Thr Ser Ala Ala
                245                 250                 255

Cys Lys Ser Ile Leu Glu Ile Met His Lys Glu Ala Gln Asp Ile Lys
            260                 265                 270
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Phe Thr Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val
        275                 280                 285

Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu Gln
    290                 295                 300

Asp Thr Asp Thr Lys Ile Thr Ile Ser Pro Leu Gln Glu Leu Thr Leu
305                 310                 315                 320

Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Asn Val Glu Thr Cys
                325                 330                 335

Ala Lys Ala Glu Glu Glu Ile Met Lys Lys Ile Arg Glu Ser Tyr Glu
            340                 345                 350

Asn Asp Ile Ala Ser Met Asn Leu Gln Ala His Leu Ile Pro Gly Leu
        355                 360                 365

Asn Leu Asn Ala Leu Gly Leu Phe Pro Pro Thr Ser Gly Met Pro Pro
    370                 375                 380

Pro Thr Ser Gly Pro Pro Ser Ala Met Thr Pro Pro Tyr Pro Gln Phe
385                 390                 395                 400

Glu Gln Ser Glu Thr Glu Thr Val His Gln Phe Ile Pro Ala Leu Ser
                405                 410                 415

Val Gly Ala Ile Ile Gly Lys Gln Gly Gln His Ile Lys Gln Leu Ser
            420                 425                 430

Arg Phe Ala Gly Ala Ser Ile Lys Ile Ala Pro Ala Glu Ala Pro Asp
        435                 440                 445

Ala Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe
    450                 455                 460

Lys Ala Gln Gly Arg Ile Tyr Gly Lys Ile Lys Glu Glu Asn Phe Val
465                 470                 475                 480

Ser Pro Lys Glu Glu Val Lys Leu Glu Ala His Ile Arg Val Pro Ser
                485                 490                 495

Phe Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu
            500                 505                 510

Leu Gln Asn Leu Ser Ser Ala Glu Val Val Val Pro Arg Asp Gln Thr
        515                 520                 525

Pro Asp Glu Asn Asp Gln Val Val Val Lys Ile Thr Gly His Phe Tyr
    530                 535                 540

Ala Cys Gln Val Ala Gln Arg Lys Ile Gln Glu Ile Leu Thr Gln Val
545                 550                 555                 560
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Lys Gln His Gln Gln Gln Lys Ala Leu Gln Ser Gly Pro Pro Gln Ser
565 570 575

Arg Arg Lys

<210> 177
<211> 401
<212> DNA
<213> Homo sapiens

<400> 177
atgccccgta aatgtcttca gtgttcttca gggtagttgg gatctcaaaa gatttggttc 60
agatccaaac aaatacacat tctgtgtttt agctcagtgt tttctaaaaa aagaaactgc 120
cacacagcaa aaaattgttt actttgttgg acaaaccaaa tcagttctca aaaaatgacc 180
ggtgcttata aaaagttata aatatcgagt agctctaaaa caaaccacct gaccaagagg 240
gaagtgagct tgtgcttagt atttacattg gatgccagtt ttgtaatcac tgacttatgt 300
gcaaactggt gcagaaattc tataaactct ttgctgtttt tgatacctgc tttttgtttc 360
attttgtttt gttttgtaaa aatgataaaa cttcagaaaa t 401

<210> 178
<211> 561
<212> DNA
<213> Homo sapiens

<400> 178
acgcctttca agggtgtacg caaagcactc attgataccc ttttggatgg ctatgaaaca 60
gcccgctatg ggacaggggt ctttggccag aatgagtacc tacgctatca ggaggccctg 120
agtgagctgg ccactgcggt taaagcacga attgggagct ctcagcgaca tcaccagtca 180
gcagccaaag acctaactca gtcccctgag gtctccccaa caaccatcca ggtgacatac 240
ctcccctcca gtcagaagag taaacgtgcc aagcacttcc ttgaattgaa gagctttaag 300
gataactata acacattgga gagtactctg tgacggagct gaaggactct tgccgtagat 360
taagccagtc agttgcaatg tgcaagacag gctgcttgcc gggccgccct cggaacatct 420
ggcccagcag gcccagactg tatccatcca agttcccgtt gtatccagag ttcttagagc 480
ttgtgtctaa agggtaattc cccaaccctt ccttatgagc atttttagaa cattggctaa 540
gactattttc ccccagtagc g 561

<210> 179
<211> 521
<212> DNA
<213> Homo sapiens

<400> 179
cccaacgcgt ttgcaaatat tcccctggta gcctacttcc ttacccccga atattggtaa 60
gatcgagcaa tggcttcagg acatgggttc tcttctcctg tgatcattca agtgctcact 120
gcatgaagac tggcttgtct cagtgtttca acctcaccag ggctgtctct tggtccacac 180
ctcgctccct gttagtgccg tatgacagcc cccatcaaat gaccttggcc aagtcacggt 240
ttctctgtgg tcaaggttgg ttggctgatt ggtggaaagt agggtggacc aaaggaggcc 300
acgtgagcag tcagcaccag ttctgcacca gcagcgcctc cgtcctagtg ggtgttcctg 360
tttctcctgg ccctgggtgg gctagggcct gattcgggaa gatgcctttg cagggagggg 420
aggataagtg ggatctacca attgattctg gcaaaacaat ttctaagatt tttttgcttt 480
atgtgggaaa cagatctaaa tctcatttta tgctgtattt t 521

<210> 180
<211> 417
<212> DNA
<213> Homo sapiens

<400> 180
ggtggaattc gccgaagatg gcggaggtgc aggtcctggt gcttgatggt cgaggccatc 60
tcctgggccg cctggcggcc atcgtggcta aacaggtact gctgggccgg aaggtggtgg 120
tcgtacgctg tgaaggcatc aacatttctg gcaatttcta cagaaacaag ttgaagtacc 180
tggctttcct ccgcaagcgg atgaacacca acccttcccg aggcccctac cacttccggg 240
cccccagccg catcttctgg cggaccgtgc gaggtatgct gccccacaaa accaagcgag 300
gccaggccgc tctggaccgt ctcaaggtgt ttgacggcat cccaccgccc tacgacaaga 360
aaaagcggat ggtggttcct gctgccctca aggtcgtgcg tctgaagcct acaagaa 417

<210> 181
<211> 283
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (35)
<223> n=A,T,C or G

<400> 181
gatttcttct aaataggatg taaaacttct ttcanattac tcttcctcag tcctgcctgc 60
caagaactca agtgtaactg tgataaaata acctttccca ggtatattgg caggtatgtg 120
tgtaatctca gaatacacag gtgacataga tatgatatga caactggtaa tggtggattc 180
atttacattg tttacacttc tatgaccagg ccttaaggga aggtcagttt tttaaaaaac 240
caagtagtgt cttcctacct atctccagat acatgtcaaa aaa 283

<210> 182
<211> 401
<212> DNA
<213> Homo sapiens

<400> 182
atattcttgc tgcttatgca gctgacattg ttgccctccc taaagcaacc aagtagcctt 60
tatttcccac agtgaaagaa aacgctggcc tatcagttac attacaaaag gcagatttca 120
agaggattga gtaagtagtt ggatggcttt cataaaaaca agaattcaag aagaggattc 180
atgctttaag aaacatttgt tatacattcc tcacaaatta tacctgggat aaaaactatg 240
tagcaggcag tgtgttttcc ttccatgtct ctctgcacta cctgcagtgt gtcctctgag 300
gctgcaagtc tgtcctatct gaattcccag cagaagcact aagaagctcc accctatcac 360
ctagcagata aaactatggg gaaaacttaa atctgtgcat a 401

<210> 183
<211> 366
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (325)
<223> n=A,T,C or G

<400> 183
accgtgtcca agtttttaga acccttgtta gccagaccga ggtgtcctgg tcaccgtttc 60
accatcatgc tttgatgttc ccctgtcttt ctctcttctg ctctcaagag caaaggttaa 120
tttaaggaca aagatgaagt cactgtaaac taatctgtca ttgtttttac cttccttttc 180
tttttcagtg cagaaattaa aagtaagtat aaagcaccgt gattgggagt gtttttgcgt 240
gtgtcggaat cactggtaaa tgttggctga gaacaatccc tccccttgca cttgtgaaaa 300
cactttgagc gctttaagag attancctga gaaataatta aatatctttt ctcttcaaaa 360
aaaaaa 366

<210> 184
<211> 370
<212> DNA
<213> Homo sapiens

<400> 184
tcttacttca aaagaaaaat aaacataaaa aataagttgc tggttcctaa caggaaaaat 60
tttaataatt gtactgagag aaactgctta cgtacacatt gcagatcaaa tatttggagt 120
taaaatgtta gtctacatag atgggtgatt gtaactttat tgccattaaa agatttcaaa 180
ttgcattcat gcttctgtgt acacataatg aaaaatgggc aaataatgaa gatctctcct 240
tcagtctgct ctgtttaatt ctgctgtctg ctcttctcta atgctgcgtc cctaattgta 300
cacagtttag tgatatctag gagtataaag ttgtcgccca tcaataaaaa tcacaaagtt 360
ggtttaaaaa 370

<210> 185
<211> 107
<212> DNA
<213> Homo sapiens

<400> 185
ctcatattat tttccttttg agaaattgga aactctttct gttgctatta tattaataaa 60
gttggtgttt attttctggt agtcaccttc cccatttaaa aaaaaaa 107

<210> 186
<211> 309
<212> DNA
<213> Homo sapiens

<400> 186
gaaaggatgg ctctggttgc cacagagctg ggacttcatg ttcttctaga gagggccaca 60
agagggccac aggggtggcc gggagttgtc agctgatgcc tgctgagagg caggaattgt 120
gccagtgagt gacagtcatg agggagtgtc tcttcttggg gaggaaagaa ggtagagcct 180
ttctgtctga atgaaaggcc aaggctacag tacagggccc cgccccagcc agggtgttaa 240
tgcccacgta gtggaggcct ctggcagatc ctgcattcca aggtcactgg actgtacgtt 300
tttatggtt 309

<210> 187
<211> 477
<212> DNA
<213> Homo sapiens

<400> 187
ttcagtccta gcaagaagcg agaattctga gatcctccag aaagtcgagc agcacccacc 60
tccaacctcg ggccagtgtc ttcaggcttt actggggacc tgcgagctgg cctaatgtgg 120

tggcctgcaa gccaggccat ccctgggcgc cacagacgag ctccgagcca ggtcaggctt 180
cggaggccac aagctcagcc tcaggcccag gcactgattg tggcagaggg gccactaccc 240
aaggtctagc taggcccaag acctagttac ccagacagtg agaagcccct ggaaggcaga 300
aaagttggga gcatggcaga cagggaaggg aaacattttc agggaaaaga catgtatcac 360
atgtcttcag aagcaagtca ggtttcatgt aaccgagtgt cctcttgcgt gtccaaaagt 420
agcccagggc tgtagcacag gcttcacagt gattttgtgt tcagccgtga gtcacac 477

<210> 188
<211> 220
<212> DNA
<213> Homo sapiens

<400> 188
taaatatggt agatattaat attcctctta gatgaccagt gattccaatt gtcccaagtt 60
ttaaataagt accctgtgag tatgagataa attagtgaca atcagaacaa gtttcagtat 120
cagatgttca agaggaagtt gctattgcat tgattttaat atttgtacat aaacactgat 180
ttttttgagc attatttttgt atttgttgta ctttaatacc 220

<210> 189
<211> 417
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (76)
<223> n=A,T,C or G
<221> unsure
<222> (77)
<223> n=A,T,C or G

<400> 189
accatcttga cagaggatac atgctcccaa aacgtttgtt accacactta aaaatcactg 60
ccatcattaa gcatcnnttt caaaattata gccattcatg atttactttt tccagatgac 120
tatcattatt ctagtccttt gaatttgtaa ggggaaaaaa aacaaaaaca aaaacttacg 180
atgcactttt ctccagcaca tcagatttca aattgaaaat taaagacatg ctatggtaat 240
gcacttgcta gtactacaca ctttgtacaa caaaaaacag aggcaagaaa caacggaaag 300
agaaaagcct tcctttgttg gcccttaaac tgagtcaaga tctgaaatgt agagatgatc 360
tctgacgata cctgtatgtt cttattgtgt aaataaaatt gctggtatga aatgaca 417

<210> 190
<211> 497
<212> DNA
<213> Homo sapiens

<400> 190
gcactgcggc gctctcccgt cccgcggtgg ttgctgctgc tgccgctgct gctgggcctg 60
aacgcaggag ctgtcattga ctggcccaca gaggagggca aggaagtatg ggattatgtg 120
acggtccgca aggatgccta catgttctgg tggctctatt atgccaccaa ctcctgcaag 180
aacttctcag aactgccccct ggtcatgtgg cttcagggcg gtccaggcgg ttctagcact 240
ggatttggaa actttgagga aattgggccc cttgacagtg atctcaaacc acggaaaacc 300
acctggctcc aggctgccag tctcctattt gtggataatc ccgtgggcac tgggttcagt 360
tatgtgaatg gtagtggtgc ctatgccaag gacctggcta tggtggcttc agacatgatg 420
gttctcctga agaccttctt cagttgccac aaagaattcc agacagttcc attctacatt 480

ttctcagagt cctatgg 497

<210> 191
<211> 175
<212> DNA
<213> Homo sapiens

<400> 191
atgttgaata ttttgcttat taactttgtt tattgtcttc tccctcgatt agaatattag 60
ctacttgagt acaaggattt gagcctgtta cattcactgc tgaattttag gctcctggaa 120
gatacccagc attcaataga gaccacacaa taaatatatg tcaaataaaa aaaaa 175

<210> 192
<211> 526
<212> DNA
<213> Homo sapiens

<400> 192
agtaaacatt attatttttt ttatatttgc aaaggaaaca tatctaatcc ttcctataga 60
aagaacagta ttgctgtaat tccttttctt ttcttcctca tttcctctgc cccttaaaag 120
attgaagaaa gagaaacttg tcaactcata tccacgttat ctagcaaagt acataagaat 180
ctatcactaa gtaatgtatc cttcagaatg tgttggttta ccagtgacac cccatattca 240
tcacaaaatt aaagcaagaa gtccatagta atttatttgc taatagtgga tttttaatgc 300
tcagagtttc tgaggtcaaa ttttatcttt tcacttacaa gctctatgat cttaaataat 360
ttacttaatg tattttggtg tattttcctc aaattaatat tggtgttcaa gactatatct 420
aattcctctg atcactttga gaaacaaact tttattaaat gtaaggcact tttctatgaa 480
ttttaaatat aaaaataaat attgttctga ttattactga aaaaaa 526

<210> 193
<211> 553
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (290)
<223> n=A,T,C or G
<221> unsure
<222> (300)
<223> n=A,T,C or G
<221> unsure
<222> (411)
<223> n=A,T,C or G
<221> unsure
<222> (441)
<223> n=A,T,C or G

<400> 193
tccattgtgg tggaattcgc tctctggtaa aggcgtgcag gtgttggccg cggcctctga 60
gctgggatga gccgtgctcc cggtggaagc aagggagccc agccggagcc atggccagta 120
cagtggtagc agttggactg accattgctg ctgcaggatt tgcaggccgt tacgttttgc 180
aagccatgaa gcatatggag cctcaagtaa aacaagtttt tcaaagccta ccaaaatctg 240
ccttcagtgg tggctattat agaggtgggt ttgaacccaa aatgacaaan cgggaagcan 300
cattaatact aggtgtaagc cctactgcca ataaagggaa aataagagat gctcatcgac 360

gaattatgct tttaaatcat cctgacaaag gaggatctcc ttatatagca nccaaaatca 420
atgaagctaa agatttacta naaggtcaag ctaaaaaatg aagtaaatgt atgatgaatt 480
ttaagttcgt attagtttat gtatatgagt actaagtttt tataataaaa tgcctcagag 540
ctacaatttt aaa 553

<210> 194
<211> 320
<212> DNA
<213> Homo sapiens

<400> 194
cccttcccaa tccatcagta aagaccccat ctgccttgtc catgccgttt cccaacaggg 60
atgtcacttg atatgagaat ctcaaatctc aatgccttat aagcattcct tcctgtgtcc 120
attaagactc tgataattgt ctcccctcca taggaatttc tcccaggaaa gaaatatatc 180
cccatctccg tttcatatca gaactaccgt ccccgatatt cccttcagag agattaaaga 240
ccagaaaaaa gtgagcctct tcatctgcac ctgtaatagt ttcagttcct attttcttcc 300
attgacccat atttatacct 320

<210> 195
<211> 320
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (203)
<223> n=A,T,C or G
<221> unsure
<222> (218)
<223> n=A,T,C or G

<400> 195
aagcatgacc tggggaaatg gtcagacctt gtattgtgtt tttggccttg aaagtagcaa 60
gtgaccagaa tctgccatgg caacaggctt taaaaaagac ccttaaaaag acactgtctc 120
aactgtggtg ttagcaccag ccagctctct gtacatttgc tagcttgtag ttttctaaga 180
ctgagtaaac ttcttatttt tanaaagggg aggctggntt gtaactttcc ttgtacttaa 240
ttgggtaaaa gtcttttcca caaaccacca tctattttgt gaactttgtt agtcatcttt 300
tatttggtaa attatgaact 320

<210> 196
<211> 357
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (36)
<223> n=A,T,C or G

<400> 196
atataaaata atacgaaact ttaaaaagca ttggantgtc agtatgttga atcagtagtt 60
tcactttaac tgtaaacaat ttcttaggac accatttggg ctagtttctg tgtaagtgta 120
aatactacaa aaacttattt atactgttct tatgtcattt gttatattca tagatttata 180
tgatgatatg acatctggct aaaaagaaat tattgcaaaa ctaaccacta tgtacttttt 240

tataaatact gtatggacaa aaaatggcat tttttatatt aaattgttta gctctggcaa 300
aaaaaaaaaa ttttaagagc tggtactaat aaaggattat tatgactgtt aaaaaaa 357

<210> 197
<211> 565
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (27)
<223> n=A,T,C or G

<400> 197
tcagctgagt accatcagga tatttanccc tttaagtgct gttttgggag tagaaaacta 60
aagcaacaat acttcctctt gacagctttg attggaatgg ggttattaga tcattcacct 120
tggtcctaca ctttttagga tgcttggtga acataacacc acttataatg aacatccctg 180
gttcctatat tttgggctat gtgggtagga attgttactt gttactgcag cagcagccct 240
agaaagtaag cccagggctt cagatctaag ttagtccaaa agctaaatga tttaaagtca 300
agttgtaatg ctaggcataa gcactctata atacattaaa ttataggccg agcaattagg 360
gaatgtttct gaaacattaa acttgtattt atgtcactaa aattctaaca caaacttaaa 420
aaatgtgtct catacatatg ctgtactagg cttcatcatg catttctaaa tttgtgtatg 480
atttgaatat atgaaagaat ttatacaaga gtgttattta aaattattaa aaataaatgt 540
atataatttg tacctattgt aaaaa 565

<210> 198
<211> 484
<212> DNA
<213> Homo sapiens

<400> 198
tatgtaagta ttggtgtctg ctttaaaaaa ggagacccag acttcacctg tccttttaa 60
acatttgaga acagtgttac tctgagcagt tgggccacct tcaccttatc cgacagctga 120
ctgttggatg tgtccattgt cgccagtttg gctgttgccc ggacaggaca ggacctccat 180
tgggcgcagc agcaggtggc aggggtgtgg cttgaggtgg gtggcagcgt ctggtcctcc 240
tctctggtgc tttctgagag ggtctctaaa gcagagtgtg gttggcctgg gggaaggcag 300
agcacgtatt tctcccctct agtacctctg catttgtgag tgttccctct ggctttctga 360
agggcagcag actcttgagt atactgcaga ggacatgctt tatcagtagg tcctgagggc 420
tccaggggct caactgacca agtaacacag aagttggggt atgtggccta tttgggtcgg 480
aaac 484

<210> 199
<211> 429
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (77)
<223> n=A,T,C or G
<221> unsure
<222> (88)
<223> n=A,T,C or G
<221> unsure

<222> (134)
<223> n=A,T,C or G
<221> unsure
<222> (151)
<223> n=A,T,C or G
<221> unsure
<222> (189)
<223> n=A,T,C or G
<221> unsure
<222> (227)
<223> n=A,T,C or G
<221> unsure
<222> (274)
<223> n=A,T,C or G
<221> unsure
<222> (319)
<223> n=A,T,C or G

<400> 199
gcttatgttt tttgttttaa cttttgtttt ttaacattta gaatattaca ttttgtatta 60
tacagtacct ttctcanaca ttttgtanaa ttcatttcgg cagctcacta ggattttgct 120
gaacattaaa aagngtgata gcgatattag ngccaatcaa atggaaaaaa ggtagtctta 180
ataaacaana cacaacgttt ttatacaaca tactttaaaa tattaanaaa actccttaat 240
attgtttcct attaagtatt attctttggg caanattttc tgatgctttt gattttctct 300
caatttagca tttgctttng gttttttttct ctatttagca ttctgttaag gcacaaaaac 360
tatgtactgt atgggaaatg ttgtaaatat tacctttttcc acattttaaa cagacaactt 420
tgaatccaa 429

<210> 200
<211> 279
<212> DNA
<213> Homo sapiens

<400> 200
gctttttga ggaattacag ggaagctcct ggaattgtac atggatatct ttatccctag 60
ggggaaatca aggagctggg cacccctaat tctttatgga agtgtttaaa actattttaa 120
ttttattaca agtattacta gagtagtggt tctactctaa gatttcaaaa gtgcatttaa 180
aatcatacat gttcccgcct gcaaatatat tgttattttg gtggagaaaa aaatagtata 240
ttctacataa aaaattaaag atattaacta agaaaaaaa 279

<210> 201
<211> 569
<212> DNA
<213> Homo sapiens

<400> 201
taggtcagta tttttagaaa ctcttaatag ctcatactct tgataccaaa agcagccctg 60
attgttaaag cacacacctg cacaagaagc agtgatggtt gcatttacat ttcctgggtg 120
cacaaaaaaa aattctcaaa aagcaaggac ttacgctttt tgcaaagcct ttgagaagtt 180
actggatcat aggaagctta taacaagaat ggaagattct taaataactc actttctttg 240
gtatccagta acagtagatg ttcaaaatat gtagctgatt aataccagca ttgtgaacgc 300
tgtacaacct tgtggttatt actaagcaag ttactactag cttctgaaaa gtagcttcat 360
aattaatgtt atttatacac tgccttccat gacttttact ttgccctaag ctaatctcca 420
aaatctgaaa tgctactcca atatcagaaa aaaaggggga ggtggaatta tatttcctgt 480

gattttaaga gtacagagaa tcatgcacat ctctgattag ttcatatatg tctagtgtgt 540
aataaaagtc aaagatgaac tctcaaaaa 569

<210> 202
<211> 501
<212> DNA
<213> Homo sapiens

<400> 202
attaataggc ttaataattg ttggcaagga tccttttgct ttctttggca tgcaagctcc 60
tagcatctgg cagtggggcc aagaaaataa ggtttatgca tgtatgatgg ttttcttctt 120
gagcaacatg attgagaacc agtgtatgtc aacaggtgca tttgagataa ctttaaatga 180
tgtacctgtg tggtctaagc tggaatctgg tcaccttcca tccatgcaac aacttgttca 240
aattcttgac aatgaaatga agctcaatgt gcatatggat tcaatcccac accatcgatc 300
atagcaccac ctatcagcac tgaaaactct tttgcattaa gggatcattg caagagcagc 360
gtgactgaca ttatgaaggc ctgtactgaa gacagcaagc tgttagtaca gaccagatgc 420
tttcttggca ggctcgttgt acctcttgga aaacctcaat gcaagatagt gtttcagtgc 480
tggcatattt tggaattctg c 501

<210> 203
<211> 261
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (36)
<223> n=A,T,C or G
<221> unsure
<222> (96)
<223> n=A,T,C or G

<400> 203
gacaagctcc tggtcttgag atgtcttctc gttaangaga tgggcctttt ggaggtaaag 60
gataaaatga atgagttctg tcatgattca ctattntata acttgcatga cctttactgt 120
gttagctctt tgaatgttct tgaaatttta gactttcttt gtaaacaaat gatatgtcct 180
tatcattgta taaaagctgt tatgtgcaac agtgtggaga ttccttgtct gatttaataa 240
aatacttaaa cactgaaaaa a 261

<210> 204
<211> 421
<212> DNA
<213> Homo sapiens

<400> 204
agcatctttt ctacaacgtt aaaattgcag aagtagctta tcattaaaaa acaacaacaa 60
caacaataac aataaatcct aagtgtaaat cagttattct acccccctacc aaggatatca 120
gcctgttttt tccctttttt ctcctgggaa taattgtggg cttcttccca aatttctaca 180
gcctctttcc tcttctcatg cttgagcttc cctgtttgca cgcatgcgtg tgcaggactg 240
gcttgtgtgc ttggactcgg ctccaggtgg aagcatgctt tcccttgtta ctgttggaga 300
aactcaaacc ttcaagccct aggtgtagcc attttgtcaa gtcatcaact gtatttttgt 360
actggcatta acaaaaaaag aagataaaat attgtaccat taaactttaa taaaacttta 420
a 421

<210> 205
<211> 460
<212> DNA
<213> Homo sapiens

<400> 205
tactctcaca atgaaggacc tggaatgaaa aatctgtgtc taaacaagtc ctctttagat 60
tttagtgcaa atccagagcc agcgtcggtt gcctcgagta attctttcat gggtaccttt 120
ggaaaagctc tcaggagacc tcacctagat gcctattcaa gctttggaca gccatcagat 180
tgtcagccaa gagcctttta tttgaaagct cattcttccc cagacttgga ctctgggtca 240
gaggaagatg ggaaagaaag gacagatttt caggaagaaa atcacatttg tacctttaaa 300
cagactttag aaaactacag gactccaaat tttcagtctt atgacttgga cacatagact 360
gaatgagacc aaaggaaaag cttaacatac tacctcaagg tgaactttta tttaaaagag 420
agagaatctt atgtttttta aatggagtta tgaattttaa 460

<210> 206
<211> 481
<212> DNA
<213> Homo sapiens

<400> 206
tgtggtggaa ttcgggacgc ccccagaccc tgacttttttc ctgcgtgggc cgtctcctcc 60
tgcggaagca gtgacctctg acccctggtg accttcgctt tgagtgcctt ttgaacgctg 120
gtcccgcggg acttggtttt ctcaagctct gtctgtccaa agacgctccg gtcgaggtcc 180
cgcctgccct gggtggatac ttgaacccca gacgcccctc tgtgctgctg tgtccggagg 240
cggccttccc atctgcctgc ccacccggag ctctttccgc cggcgcaggg tcccaagccc 300
acctcccgcc ctcagtcctg cggtgtgcgt ctgggcacgt cctgcacaca caatgcaagt 360
cctggcctcc gcgcccgccc gcccacgcga gccgtacccg ccgccaactc tgttatttat 420
ggtgtgaccc cctggaggtg ccctcggccc accggggcta tttattgttt aatttatttg 480
t 481

<210> 207
<211> 605
<212> DNA
<213> Homo sapiens

<400> 207
acccttttg gattcagggc tcctcacaat taaaatgagt gtaatgaaac aaggtgaaaa 60
tatagaagca tccctttgta tactgttttg ctacttacag tgtacttggc attgctttat 120
ctcactggat tctcacggta ggatttctga gatcttaatc taagctccaa agttgtctac 180
ttttttgatc ctagggtgct ccttttgttt tacagagcag ggtcacttga tttgctagct 240
ggtggcagaa ttggcaccat tacccaggtc tgactgacca ccagtcagag gcactttatt 300
tgtatcatga aatgatttga aatcattgta aagcagcgaa gtctgataat gaatgccagc 360
tttccttgtg ctttgataac aaagactcca aatattctgg agaacctgga taaaagtttg 420
aagggctaga ttgggatttg aagacaaaat tgtaggaaat cttacatttt tgcaataaca 480
aacattaatg aaagcaaaac attataaaag taattttaat tcaccacata cttatcaatt 540
tcttgatgct tccaaatgac atctaccaga tatggttttg tggacatctt tttctgttta 600
cataa 605

<210> 208
<211> 655
<212> DNA
<213> Homo sapiens

<400> 208
ggcgttgttc tggattcccg tcgtaactta aagggaaact ttcacaatgt ccggagccct 60
tgatgtcctg caaatgaagg aggaggatgt ccttaagttc cttgcagcag gaacccactt 120
aggtggcacc aatcttgact tccagatgga acagtacatc tataaaagga aaagtgatgg 180
catctatatc ataaatctca agaggacctg ggagaagctt ctgctggcag ctcgtgcaat 240
tgttgccatt gaaaaccctg ctgatgtcag tgttatatcc tccaggaata ctggccagag 300
ggctgtgctg aagtttgctg ctgccactgg agccactcca attgctggcc gcttcactcc 360
tggaaccttc actaaccaga tccaggcagc cttccgggag ccacggcttc ttgtggttac 420
tgaccccagg gctgaccacc agcctctcac ggaggcatct tatgttaacc tacctaccat 480
tgcgctgtgt aacacagatt ctcctctgcg ctatgtggac attgccatcc catgcaacaa 540
caagggagct cactcagtgg gtttgatgtg gtggatgctg gctcgggaag ttctgcgcat 600
gcgtggcacc atttcccgtg aacacccatg ggaggtcatg cctgatctgt acttc 655

<210> 209
<211> 621
<212> DNA
<213> Homo sapiens

<400> 209
catttagaac atggttatca tccaagacta ctctaccctg caacattgaa ctcccaagag 60
caaatccaca ttcctcttga gttctgcagc ttctgtgtaa atagggcagc tgtcgtctat 120
gccgtagaat cacatgatct gaggaccatt catggaagct gctaaatagc ctagtctggg 180
gagtcttcca taaagttttg catggagcaa acaaacagga ttaaactagg tttggttcct 240
tcagccctct aaaagcatag ggcttagcct gcaggcttcc ttgggctttc tctgtgtgtg 300
tagttttgta aacactatag catctgttaa gatccagtgt ccatggaaac cttcccacat 360
gccgtgactc tggactatat cagtttttgg aaagcagggt tcctctgcct gctaacaagc 420
ccacgtggac cagtctgaat gtctttcctt tacacctatg tttttaaata gtcaaacttc 480
aagaaacaat ctaaacaagt ttctgttgca tatgtgtttg tgaacttgta tttgtattta 540
gtaggcttct atattgcatt taacttgttt ttgtaactcc tgattcttcc ttttcggata 600
ctattgatga ataaagaaat t 621

<210> 210
<211> 533
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (20)
<223> n=A,T,C or G
<221> unsure
<222> (21)
<223> n=A,T,C or G
<221> unsure
<222> (61)
<223> n=A,T,C or G

<400> 210
cgccttgggg agccggcggn ngagtccggg acgtggagac ccggggtccc ggcagccggg 60
nggcccgcgg gcccagggtg gggatgcacc gccgcggggt gggagctggc gccatcgcca 120
agaagaaact tgcagaggcc aagtataagg agcgagggac ggtcttggct gaggaccagc 180
tagcccagat gtcaaagcag ttggacatgt tcaagaccaa cctggaggaa tttgccagca 240
aacacaagca ggagatccgg aagaatcctg agttccgtgt gcagttccag gacatgtgtg 300
caaccattgg cgtggatccg ctggcctctg gaaaaggatt ttggtctgag atgctgggcg 360

tgggggactt ctattacgaa ctaggtgtcc aaattatcga agtgtgcctg gcgctgaagc 420
atcggaatgg aggtctgata actttggagg aactacatca acaggtgttg aagggaaggg 480
gcaagttcgc ccaggatgtc agtcaagatg acctgatcag agccatcaag aaa 533

<210> 211
<211> 451
<212> DNA
<213> Homo sapiens

<400> 211
ttagcttgag ccgagaacga ggcgagaaag ctggagaccg aggagaccgc ctagagcgga 60
gtgaacgggg aggggaccgt ggggaccggc ttgatcgtgc gcggacacct gctaccaagc 120
ggagcttcag caaggaagtg gaggagcgga gtagagaacg gccctcccag cctgaggggc 180
tgcgcaaggc agctagcctc acggaggatc gggaccgtgg gcgggatgcc gtgaagcgag 240
aagctgccct acccccagtg agccccctga aggcggctct ctctgaggag gagttagaga 300
agaaatccaa ggctatcatt gaggaatatc tccatctcaa tgacatgaaa gaggcagtcc 360
agtgcgtgca ggagctggcc tcaccctcct tgctcttcat ctttgtacgg catggtgtcg 420
agtctacgct ggagcgcagt gccattgctc g 451

<210> 212
<211> 471
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (54)
<223> n=A,T,C or G

<400> 212
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gggcaacatt ccacagctgc cctggctgtg atgagtgtcc ttgcaggggc cggagtagga 120
gcactggggt gggggcggaa ttggggttac tcgatgtaag ggattccttg ttgttgtgtt 180
gagatccagt gcagttgtga tttctgtgga tcccagcttg gttccaggaa ttttgtgtga 240
ttggcttaaa tccagttttc aatcttcgac agctgggctg gaacgtgaac tcagtagctg 300
aacctgtctg acccggtcac gttcttggat cctcagaact ctttgctctt gtcggggtgg 360
gggtgggaac tcacgtgggg agcggtggct gagaaaatgt aaggattctg gaatacatat 420
tccatgggac tttccttccc tctcctgctt cctcttttcc tgctccctaa c 471

<210> 213
<211> 511
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (27)
<223> n=A,T,C or G
<221> unsure
<222> (63)
<223> n=A,T,C or G
<221> unsure
<222> (337)
<223> n=A,T,C or G

<221> unsure
<222> (442)
<223> n=A,T,C or G

<400> 213
ctaattagaa acttgctgta ctttttnttt tcttttaggg gtcaaggacc ctctttatag 60
ctnccatttg cctacaataa attattgcag cagtttgcaa tactaaaata ttttttatag 120
actttatatt tttccttttg ataaagggat gctgcatagt agagttggtg taattaaact 180
atctcagccg tttccctgct ttcccttctg ctccatatgc ctcattgtcc ttccagggag 240
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taactcttcc cactgcatat ttccatcttg aattggnggt tctaaattct gaaactgtag 360
ttgagataca gctatttaat atttctggga gatgtgcatc cctcttcttt gtggttgccc 420
aaggttgttt tgcgtaactg anactccttg atatgcttca gagaatttag gcaaacactg 480
gccatggccg tgggagtact gggagtaaaa t 511

<210> 214
<211> 521
<212> DNA
<213> Homo sapiens

<400> 214
agcattgcca aataatccct aattttccac taaaaatata atgaaatgat gttaagcttt 60
ttgaaaagtt taggttaaac ctactgttgt tagattaatg tatttgttgc ttccctttat 120
ctggaatgtg gcattagctt ttttatttta accctcttta attcttattc aattccatga 180
cttaaggttg gagagctaaa cactgggatt tttggataac agactgacag ttttgcataa 240
ttataatcgg cattgtacat agaaaggata tggctacctt ttgttaaatc tgcactttct 300
aaatatcaaa aaagggaaat gaagtataaa tcaatttttg tataatctgt ttgaaacatg 360
agttttattt gcttaatatt agggctttgc ccctttctg taagtctctt gggatcctgt 420
gtagaagctg ttctcattaa acaccaaaca gttaagtcca ttctctggta ctagctacaa 480
attcggtttc atattctact taacaattta aataaactga a 521

<210> 215
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (17)
<223> n=A,T,C or G
<221> unsure
<222> (20)
<223> n=A,T,C or G
<221> unsure
<222> (60)
<223> n=A,T,C or G
<221> unsure
<222> (61)
<223> n=A,T,C or G
<221> unsure
<222> (365)
<223> n=A,T,C or G

<400> 215

gagcggagag cggaccngtn agagccctga gcagccccac cgccgccgcc ggcctagttn 60
ncatcacacc ccgggaggag ccgcagctgc cgcagccggc cccagtcacc atcaccgcaa 120
ccatgagcag cgaggccgag acccagcagc cgcccgccgc ccccccccgcc gccccgcccc 180
tcagcgccgc cgacaccaag cccggcacta cgggcagcgg cgcagggagc ggtggcccgg 240
gcggcctcac atcggcggcg cctgccggcg gggacaagaa ggtcatcgca acgaaggttt 300
tgggaacagt aaaatggttc aatgtaagga acggatatgg tttcatcaac aggaatgaca 360
ccaangaaga tgtatttgta c 381

<210> 216
<211> 425
<212> DNA
<213> Homo sapiens

<400> 216
ttactaacta ggtcattcaa ggaagtcaag ttaacttaaa catgtcacct aaatgcactt 60
gatggtgttg aaatgtccac cttcttaaat ttttaagatg aacttagttc taaagaagat 120
aacaggccaa tcctgaaggt actccctgtt tgctgcagaa tgtcagatat tttggatgtt 180
gcataagagt cctatttgcc ccagttaatt caacttttgt ctgcctgttt tgtggactgg 240
ctggctctgt tagaactctg tccaaaaagt gcatggaata taacttgtaa agcttcccac 300
aattgacaat atatatgcat gtgtttaaac caaatccaga aagcttaaac aatagagctg 360
cataatagta tttattaaag aatcacaact gtaaacatga gaataactta aggattctag 420
tttag 425

<210> 217
<211> 181
<212> DNA
<213> Homo sapiens

<400> 217
gagaaaccaa atgataggtt gtagagcctg atgactccaa acaaagccat cacccgcatt 60
cttcctcctt cttctggtgc tacagctcca agggcccttc accttcatgt ctgaaatgga 120
actttggctt tttcagtgga agaatatgtt gaaggtttca ttttgttcta gaaaaaaaaa 180
a 181

<210> 218
<211> 405
<212> DNA
<213> Homo sapiens

<400> 218
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agtgatacca tcaagcctga tgtccaaaag agcaaagaat atttctccaa gcagaagtga 120
gcgctgggct gttttagtgc caggctgcgg tgggcagcca tgagaacaaa acctcttctg 180
tatttttttt ttccattagt aaaacacaag acttcagatt cagccgaatt gtggtgtctt 240
acaaggcagg cctttcctac agggggtgga gagaccagcc tttcttcctt tggtaggaat 300
ggcctgagtt ggcgttgtgg gcaggctact ggtttgtatg atgtattagt agagcaaccc 360
attaatcttt tgtagtttgt attaaacttg aactgagaaa aaaaa 405

<210> 219
<211> 216
<212> DNA
<213> Homo sapiens

<220>

<221> unsure
<222> (207)
<223> n=A,T,C or G
<221> unsure
<222> (210)
<223> n=A,T,C or G

<400> 219
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tcaattgtaa acttcttgtt aagactgtta cgtttctatt gcttttgtat gggatattgc 180
aaaaataaaa aggaaagaac cctcttnaan aaaaaa 216

<210> 220
<211> 380
<212> DNA
<213> Homo sapiens

<400> 220
cttacaaatt gcccccatgt gtaggggaca cagaaccctt tgagaaaact tagatttttg 60
tctgtacaaa gtctttgcct ttttccttct tcatttttt ccagtacatt aaatttgtca 120
atttcatctt tgagggaaac tgattagatg ggttgtgttt gtgttctgat ggagaaaaca 180
gcaccccaag gactcagaag atgattttaa cagttcagaa cagatgtgtg caatattggt 240
gcatgtaata atgttgagtg gcagtcaaaa gtcatgattt ttatcttagt tcttcattac 300
tgcattgaaa aggaaaacct gtctgagaaa atgcctgaca gtttaattta aaactatggt 360
gtaagtcttt gacaaaaaaa 380

<210> 221
<211> 398
<212> DNA
<213> Homo sapiens

<400> 221
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tgtatattta atgaatgaac atgtacaatt tgccactggg aggaggttcc tttttgttgg 120
gtgagtctgc aagtgaattt cactgatgtt gatattcatt gtgtgtagtt ttatttcggt 180
cccagccccg tttcctttta ttttggagct aatgccagct gcgtgtctag ttttgagtgc 240
agtaaaatag aatcagcaaa tcactcttat ttttcatcct tttccggtat tttttgggtt 300
gtttctgtgg gagcagtgta caccaactct tcctgtatat tgccttttg ctggaaaatg 360
ttgtatgttg aataaaattt tctataaaaa ttaaaaaa 398

<210> 222
<211> 301
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (49)
<223> n=A,T,C or G
<221> unsure
<222> (64)
<223> n=A,T,C or G

<400> 222
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taanaacttg aaacttgtaa actgagatgt ctgtagcttt tttgcccatc tgtagtgtat 120
gtgaagattt caaaacctga gagcactttt tctttgttta gaattatgag aaaggcacta 180
gatgacttta ggatttgcat ttttcccttt attgcctcat ttcttgtgac gccttgttgg 240
ggagggaaat ctgtttattt tttcctacaa ataaaaagct aagattctat atcgcaaaaa 300
a 301

<210> 223
<211> 200
<212> DNA
<213> Homo sapiens

<400> 223
gtaagtgctt aggaagaaac tttgcaaaca tttaatgagg atacactgtt cattttaaa 60
attccttcac actgtaattt aatgtgtttt atattctttt gtagtaaaac aacataactc 120
agatttctac aggagacagt ggttttattt ggattgtctt ctgtaatagg tttcaataaa 180
gctggatgaa cttaaaaaaa 200

<210> 224
<211> 385
<212> DNA
<213> Homo sapiens

<400> 224
gaaaggtttg atccggactc aaagaaagca aaggagtgtg agccgccatc tgctggagca 60
gctgtaactg caagacctgg acaagagatt cgtcagcgaa ctgcagctca aagaaacctt 120
tctccaacac cagcaagccc taaccagggc cctcctccac aagttccagt atctcctgga 180
ccaccaaagg acagttctgc ccctggtgga cccccagaaa ggactgttac tccagcccta 240
tcatcaaatg tgttaccaag acatcttgga tcccctgcta cttcagtgcc tggaatgggt 300
aaacagagca cttaatgtta tttacagttt atattgtttt ctctggttac caataaaacg 360
ggccattttc aggtggtaaa aaaaa 385

<210> 225
<211> 560
<212> PRT
<213> Homo sapien

<400> 225

Met	Glu	Cys	Leu	Tyr	Tyr	Phe	Leu	Gly	Phe	Leu	Leu
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Leu	Ala	Ala	Arg	Leu	Pro	Leu	Asp	Ala	Ala	Lys	Arg
			20				25				30
Phe	His	Asp	Val	Leu	Gly	Asn	Glu	Arg	Pro	Ser	Ala
			35				40				45
Tyr	Met	Arg	Glu	His	Asn	Gln	Leu	Asn	Gly	Trp	Ser
			50				55				60
Ser	Asp	Glu	Asn	Asp	Trp	Asn	Glu	Lys	Leu	Tyr	Pro
65					70				75		80
Val	Trp	Lys	Arg	Gly	Asp	Met	Arg	Trp	Lys	Asn	Ser
			85				90				95
Trp	Lys	Gly	Gly	Arg	Val	Gln	Ala	Val	Leu	Thr	Ser
			100				105				110
Asp	Ser	Pro	Ala	Leu	Val	Gly	Ser	Asn	Ile	Thr	Phe
			115				120				125
Ala	Val	Asn	Leu	Ile	Phe	Pro	Arg	Cys	Gln	Lys	Glu
			130				135				140
Asp	Ala	Asn	Gly	Asn	Leu	Leu	Asp	Leu	Val	Arg	Gly
145					150				155		160
Tyr	Val	His	Gln	Leu	Gln	Asp	Asp	Asp	Leu	Gly	Arg
			165				170				175
Leu	Leu	Lys	Gly	Gln	Pro	Ser	Leu	Arg	Ala	Met	Ala
			180				185				190
Met	Phe	Gly	Leu	Lys	Val	Thr	Leu	Gln	Leu	Pro	Pro
			195				200				205
Leu	Leu	Phe	Leu	Gln	Leu	Arg	Asp	Thr	Phe	Pro	Gly
			210				215				220
Asp	Gln	Leu	Leu	Leu	Thr	Ala	Leu	Glu	Leu	Phe	Gln
225					230				235		240
Leu	Pro	His	Pro	Leu	Leu	Gln	Ser	Ala	Ala	Leu	Gln
			245				250				255
Ala	Leu	Gln	Gln	Trp	Leu	Gly	Asn	Val	Pro	Leu	Leu
			260				265				270
Met	Leu	Leu	Gln	Asp	Ile	Gln	Thr	Glu	Glu	Ala	Phe
			275				280				285
Val	Leu	Ala	Leu	Arg	Leu	Pro	Gly	Leu	Cys	Gln	Arg
			290				295				300
Leu	Gly	Leu	Asp	Leu	Leu	Arg	Leu	Asn	Leu	Arg	Leu
305					310				315		320
Cys	Leu	Ser	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Ala	Arg
			325				330				335
Ala	Phe	Pro	Pro	Asn	Leu	Leu	Gly	Glu	Leu	Thr	Ala
			340				345				350
Leu	Arg	Thr	Leu	Thr	Leu	Arg	Gly	Asn	Leu	Ala	Ser
			355				360				365
Leu	Pro	Ala	Gly	Val	Leu	Gln	Gly	Leu	Gly	Ala	Leu
			370				375				380
Asp	Arg	Leu	Glu	Leu	Leu	Asp	Leu	Arg	Gly	Asn	Cys
385					390				395		400
Leu	Arg	Ala	Leu	Pro	Ala	Gln	Leu	Ala	Ala	Leu	Leu
			405				410				415
Arg	Leu	Asp	Leu	Leu	Leu	Leu	Ser	Leu	Asp	Leu	Leu
			420				425				430
Ser	Ala	Ala	Gly	Pro	Gly	Leu	Val	Leu	Leu	Leu	Arg
			435				440				445
Ala	Ala	Glu	Leu	Ala	His	Leu	Pro	Arg	Gly	Glu	Arg
			450				455				460
Leu	Arg	Arg	Leu	Ser	Leu	Gln	Gly	Cys	Arg	Leu	Ala
465					470				475		480
Ala	Leu	Gly	Pro	Ala	Leu	Gly	Gln	Leu	Pro	Thr	Leu
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Gln	Thr	Leu	Ser	Leu	Ala	Gln	Asn	Gln	Leu	Ala	Ser
			500				505				510
Leu	Pro	Leu	Gly	Val	Leu	Val	Ala	Ala	Pro	Glu	Leu
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Gln	Ala	Leu	Asp	Leu	Ser	His	Asn	Ala	Leu	Arg	Ser
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Leu	Asp	Pro	Val	Leu	Leu	Glu	Thr	Leu	Pro	Glu	Leu
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Asn Ile Val Tyr Glu Lys Asn Cys Arg Asn Glu Ala Gly Leu Ser Ala
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Asp Pro Tyr Val Tyr Asn Trp Thr Ala Trp Ser Glu Asp Ser Asp Gly
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145                 150                 155                 160
Pro Phe Pro His His Pro Gly Trp Arg Arg Trp Asn Phe Ile Tyr Val
                165                 170                 175
Phe His Thr Leu Gly Gln Tyr Phe Gln Lys Leu Gly Arg Cys Ser Val
            180                 185                 190
Arg Val Ser Val Asn Thr Ala Asn Val Thr Leu Gly Pro Gln Leu Met
        195                 200                 205
Glu Val Thr Val Tyr Arg Arg His Gly Arg Ala Tyr Val Pro Ile Ala
    210                 215                 220
Gln Val Lys Asp Val Tyr Val Val Thr Asp Gln Ile Pro Val Phe Val
225                 230                 235                 240
Thr Met Phe Gln Lys Asn Asp Arg Asn Ser Ser Asp Glu Thr Phe Leu
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Lys Asp Leu Pro Ile Met Phe Asp Val Leu Ile His Asp Pro Ser His
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Phe Leu Asn Tyr Ser Thr Ile Asn Tyr Lys Trp Ser Phe Gly Asp Asn
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Thr Gly Leu Phe Val Ser Thr Asn His Thr Val Asn His Thr Tyr Val
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Leu Asn Gly Thr Phe Ser Leu Asn Leu Thr Val Lys Ala Ala Ala Pro
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Gly Pro Cys Pro Pro Pro Pro Pro Pro Pro Arg Pro Ser Lys Pro Thr
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Pro Ser Leu Gly Pro Ala Gly Asp Asn Pro Leu Glu Leu Ser Arg Ile
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Pro Asp Glu Asn Cys Gln Ile Asn Arg Tyr Gly His Phe Gln Ala Thr
        355                 360                 365
Ile Thr Ile Val Glu Gly Ile Leu Glu Val Asn Ile Ile Gln Met Thr
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Asp Val Leu Met Pro Val Pro Trp Pro Glu Ser Ser Leu Ile Asp Phe
385                 390                 395                 400
Val Val Thr Cys Gln Gly Ser Ile Pro Thr Glu Val Cys Thr Ile Ile
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Ser Asp Pro Thr Cys Glu Ile Thr Gln Asn Thr Val Cys Ser Pro Val
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Asp Val Asp Glu Met Cys Leu Leu Thr Val Arg Arg Thr Phe Asn Gly
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Ser Gly Thr Tyr Cys Val Asn Leu Thr Leu Gly Asp Asp Thr Ser Leu
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Ala Leu Thr Ser Thr Leu Ile Ser Val Pro Asp Arg Asp Pro Ala Ser
465                 470                 475                 480
Pro Leu Arg Met Ala Asn Ser Ala Leu Ile Ser Val Gly Cys Leu Ala
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Ile Phe Val Thr Val Ile Ser Leu Leu Val Tyr Lys Lys His Lys Glu
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Tyr Asn Pro Ile Glu Asn Ser Pro Gly Asn Val Val Arg Ser Lys Gly
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Leu Ser Val Phe Leu Asn Arg Ala Lys Ala Val Phe Phe Pro Gly Asn
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Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Ile Thr
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Pro Glu Ala Phe Glu Lys Leu Gly Phe Pro Ala Ala Lys Glu Ile Ala
            100                 105                 110
Asn Met Cys Arg Phe Tyr Glu Met Lys Pro Asp Arg Asp Val Asn Leu
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cagggagata tttacgttct caccccaaat ttccacgaat ggacctgaac atcagccaaa 7560
tggagaaaca catgaaagcc acagaattta tgttgcaata cgagcaatgg ataggaactc 7620
cttacagtct gctgtatcta acattgccca ggcgcctctg tttattcccc ccaattctga 7680
tcctgtacct gccagagatt atcttatatt gaaaggagtt ttaacagcaa tgggtttgat 7740
aggaatcatt tgccttatta tagttgtgac acatcatact ttaagcagga aaaagagagc 7800
agacaagaaa gagaatggaa caaaattatt ataatgaatt ctgcagatat ccatcacact 7860
ggcggccgct cgagcaccac caccaccacc actgagatcc ggctgctaac aaagcccgaa 7920
aggaagctga gttggctgct gccaccgctg agcaataact agcataaccc cttggggcct 7980
ctaaacgggt cttgaggggt tttttgctga aaggaggaac tatatccgga t 8031

<210> 255
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 255
gtggccagng actagaaggc gaggcgccgc gggaccatgg cggcggcggc ggacgagcgg 60
agtccanagg acggagaaga cgaggaagag gaggagcagt tggttctggt ggaattatca 120
ggaattattg attcagactt cctctcaaaa tgtgaaaata aatgcaaggt tttgggcatt 180
gacactgaga ggcccattct gcaagtggac agctgtgtct ttgctgggga gtatgaagac 240
actctangga cctgtgttat atttgaagaa aatgntnaac atgctgatac agaaggcaat 300
aataaaacag tgctaaaata taaatgccat acaatgaaga agctcagcat gacaagaact 360
ctcctgacag agaagaagga aggagaagaa aacatangtg g 401

<210> 256
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 256
tggtggncct gggatgggga accgcggtgg cttccgngga ggtttcggca ntggcatccg 60
gggccggggt cgcggccgng gacggggccg gggccnangc cgnnganctc gcggangcaa 120
ggccgaggat aaggagtgga tgcccgtcac caacttgggc cgcttgncca aggacatgaa 180
nancaagccc ctgnaggaga tctatntctt cttccctgcc ccattaagga atcaagagat 240
catttgattt cttcctgggg gcctctctca aggatnaggt ttttgaagat tatgccagtg 300
canaaannan accccgttgc ccngtccatc tncacccaac ncttccaagg gcnatttttg 360
tttaggcctc attncngggg ggaaccttaa cccaatttgg g 401

<210> 257
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 257
atgtatgtaa aacacttcat aaaatgtaaa gggctataac aaatatgtta taaagtgatt 60
ctctcagccc tgaggtatac agaatcattt gcctcagact gctgttggat tttaaaattt 120
ttaaaatatc tgctaagtaa tttgctatgt cttctcccac actatcaata tgcctgcttc 180
taacaggctc cccactttct tttaatgtgc tgttatgagc tttggacatg agataaccgt 240
gcctgttcag agtgtctaca gtaagagctg gacaaactct ggagggacac agtctttgag 300
acagctcttt tggttgcttt ccacttttct gaaaggttca cagtaacctt ctagataata 360
gaaactccca gttaaagcct angctancaa ttttttttag t 401

<210> 258
<211> 401
<212> DNA
<213> Homo sapien

<400> 258
ggagcgctag gtcggtgtac gaccgagatt agggtgcgtg ccagctccgg gaggccgcgg 60
tgaggggccg ggcccaagct gccgacccga gccgatcgtc agggtcgcca gcgcctcagc 120
tctgtggagg agcagcagta gtcggagggt gcaggatatt agaaatggct actccccagt 180
caattttcat ctttgcaatc tgcattttaa tgataacaga attaattctg gcctcaaaaa 240
gctactatga tatcttaggt gtgccaaaat cggcatcaga gcgccaaatc aagaaggcct 300
ttcacaagtt ggccatgaag taccaccctg acaaaaataa gacccagatg ctgaagcaaa 360
attcagagag attgcagaag catatgaaac actctcagat g 401

<210> 259
<211> 401
<212> DNA
<213> Homo sapien

<400> 259
attgggtttg gagggaggat gatgacagag gaatgccctt tggccatcac ggttttgatt 60
ctccagaata ttgtgggttt gatcatcaat gcagtcatgt taggctgcat tttcatgaaa 120
acagctcagg ctcacagaag ggcagaaact ttgattttca gccgccatgc tgtgattgcc 180
gtccgaaatg gcaagctgtg cttcatgttc cgagtgggtg acctgaggaa aagcatgatc 240
attagtgcct ctgtgcgcat ccaggtggtc aagaaaacaa ctacacctga aggggaggtg 300
gttcctattc accaactgga cattcctgtt gataacccaa tcgagagcaa taacatttt 360
ctggtggccc ctttgatcat ctgccacgtg attgacaagc g 401

<210> 260
<211> 363
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(363)
<223> n = A,T,C or G

<400> 260
aggaganang gaggggana tgaataggga tggagaggga natagtggat gagcagggca 60
canggagagg aancagaaag gagaggcaag acagggagac acacancaca nangangana 120
caggtggggg ctggggtggg gcatggagag cctttnangt cncccaggcc accctgctct 180
cgctggnctg ttgaaaccca ctccatggct tcctgccact gcagttgggc ccagggctgg 240
cttattnctg gaatgcaagt ggctgtggct tggagcctcc cctctggnnn anggaaannn 300
attgctccct tatctgcttg gaatatctga gtttttccan cccggaaata aaacacacac 360
aca 363

<210> 261
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 261
cggctctccg ccgctctccc ggggtttcgg ggcacttggg tcccacagtc tggtcctgct 60
tcaccttccc ctgacctgag tagtcgccat ggcacaggtt ctcagaggca ctgngactga 120
cttccctgga tttgatgagc gggctgatgc anaaactctt cggaaggcta tgaaaggctt 180
gggcacagat gaggagagca tcctgactct gttgacatcc cgaagtaatg ctcagcgcca 240
ggaaatctct gcagctttta agactctgtt tggcagggat cttctggatg acctgaaatc 300
agaactaact ggaaaatttg aaaaattaat tgtggctctg atgaaaccct ctcggcttta 360
tgatgcttat gaactgaaac atgccttgaa gggagctgga a 401

<210> 262
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 262
agtctanaac atttctaata ttttgngctt tcatatatca aaggagatta tgtgaaacta 60
tttttaaata ctgtaaagtg acatatagtt ataagatata tttctgtaca gtagagaaag 120
agtttataac atgaagaata ttgtaccatt atacattttc attctcgatc tcataagaaa 180
ttcaaaagaa taatgataga ggtgaaaata tgtttacttt ctctaaatca agcctagttg 240
tcaactcaaa aattatgntg catagtttta ttttgaattt aggttttggg actacttttt 300
tccancttca atgagaaaat aaaatctaca actcaggagt tactacagaa gttctaanta 360
ttttttgct aannagcnaa aaatataaac atatgaaaat g 401

<210> 263
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 263
ctgtccgacc aagagaggcc ggccgagccc gaggcttggg cttttgcttt ctggcggagg 60
gatctgcggc ggtttaggag gcggcgctga tcctgggagg aagaggcagc tacggcggcg 120
gcggcggtgg cggctagggc ggcggcgaat aaaggggccg ccgccgggtg atgcggtgac 180
cactgcggca ggcccaggag ctgagtgggc cccggccctc agcccgtccc gncggacccg 240
ctttcctcaa ctctccatct tctcctgccg accgagatcg ccgaggcggn ctcaggctcc 300
ctanccccct ccccgtccct tccccncccc cgtccccgcc ccgggggccg ccgccacccg 360
cctcccacca tggctctgaa ganaatccac aaggaattga a 401

<210> 264
<211> 401
<212> DNA
<213> Homo sapien

<400> 264
aacaccagcc actccaggac ccctgaaggc ctctaccagg tcaccagtgt tctgcgccta 60
aagccacccc ctggcagaaa cttcagctgt gtgttctgga atactcacgt gagggaactt 120
actttggcca gcattgacct tcaaagtcag atggaaccca ggacccatcc aacttggctg 180
cttcacattt tcatcccctc ctgcatcatt gctttcattt tcatagccac agtgatagcc 240
ctaagaaaac aactctgtca aaagctgtat tcttcaaaag acacaacaaa aagacctgtc 300
accacaacaa agagggaagt gaacagtgct gtgaatctga acctgtggtc ttgggagcca 360
gggtgacctg atatgacatc taaagaagct tctggactct g 401

<210> 265
<211> 271
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(271)
<223> n = A,T,C or G

<400> 265
gccacttcct gtggacatgg gcagagcgct gctgccagtt cctggtagcc ttgaccacna 60
cgctgggggg tctttgtgat ggtcatgggt ctcatttgca cttgggggtg tgggattcaa 120
gttagaagtt tctagatctg gccgggcgca gtggctcaca cctgtaatcc cagcacttta 180
ggaggctgag gcaggcggat catgaggtca ggagatcgag accgtcctgg ctaacacagt 240
gaaaccccgt ctctactaaa aatacaaaaa a 271

<210> 266
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)

<223> n = A,T,C or G

<400> 266
attcataaat ttagctgaaa gatactgatt caatttgtat acagngaata taaatgagac 60
gacagcaaaa ttttcatgaa atgtaaaata tttttatagt ttgttcatac tatatgaggt 120
tctattttaa atgactttct ggattttaaa aaatttcttt aaatacaatc atttttgtaa 180
tatttatttt atgcttatga tctagataat tgcagaatat cattttatct gactctgtct 240
tcataagaga gctgtggccg aattttgaac atctgttata gggagtgatc aaattagaag 300
gcaatgtgga aaaacaattc tgggaaagat ttctttatat gaagtccctg ccactagcca 360
gccatcctaa ttgatgaaag ttatctgttc acaggcctgc a 401

<210> 267
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 267
gaagaggcat cacctgatcc cggagacctt tggagttaag aggcggcgga agcgagggcc 60
tgtggagtcg gatcctcttc ggggtgagcc agggtcggcg cgcgcggctg tctcanaact 120
catgcagctg ttcccgcgag gcctgtttga ggacgcgctg ccgcccatcg tgctgaggag 180
ccaggtgtac agccttgtgc ctgacaggac cgtggccgac cggcagctga aggagcttca 240
agagcanggg gagacaaaat cgtccagctg ggcttcnact tggatgccca tggaanttat 300
tctttcnctt ganggactta cnngggaccc aagaanccct tncaaggggc ccttngtgga 360
tgggncccga aaccccnnta tttgcccttg ggggggncca a 401

<210> 268
<211> 223
<212> DNA
<213> Homo sapien

<400> 268
tcgccatgtt ggccaggctg gtcttgaact cctgacttta agtgatccac ccgcctcaac 60
ctcccaaagt gctgggatta caggtgtgag ccaccgcgcc tggcctgata catactttta 120
gaatcaagta gtcacgcact ttttctgttc atttttctaa aaagtaaata tacaaatgtt 180
ttgttttttg ttttttttgt ttgtttgttt ctgttttttt ttt 223

<210> 269
<211> 401
<212> DNA
<213> Homo sapien

<400> 269
actatgtaaa ccacattgta ctttttttta ctttggcaac aaatatttat acatacaaga 60
tgctagttca tttgaatatt tctcccaact tatccaagga tctccagctc taacaaaatg 120
gtttatttt atttaaatgt caatagttgt tttttaaaat ccaaatcaga ggtgcaggcc 180
accagttaaa tgccgtctat caggttttgt gccttaagag actacagagt caaagctcat 240
ttttaaagga gtaggacaaa gttgtcacag gtttttgttg ttgtttttat tgcccccaaa 300
attacatgtt aatttccatt tatatcaggg attctattta cttgaagact gtgaagttgc 360
cattttgtct cattgttttc tttgacataa ctaggatcca t 401

<210> 270
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 270
tggctgttga ttcacctcag cactgcttgg tatctgcacc ctacctctct ttagaggctg 60
ccttgtcaac tgaaaaatgc acctgacttc gagcaagact ctttccttag gttctggatc 120
tgtttgagcc ccatggcact gagctggaat ctgagggtct tgttccaagg atgtgatgat 180
gtgggagaat gttctttgaa agagcagaaa tccagtctgc atggaaacag cctgtagagn 240
agaagtttcc agtgataagt gttcactgtt ctaaggaggt acaccacagc tacctgaatt 300
ttcccaaaat gagtgcttct gtgcgttaca actggccttt gtacttgact gtgatgactt 360
tgttttttct tttcaattct anatgaacat gggaaaaaat g 401

<210> 271
<211> 329
<212> DNA
<213> Homo sapien

<400> 271
ccacagcctc caagtcaggt ggggtggagt cccagagctg cacagggttt ggcccaagtt 60
tctaagggag gcacttcctc ccctcgccca tcagtgccag cccctgctgg ctggtgcctg 120
agcccctcag acagcccccc gccccgcagg cctgccttct cagggacttc tgcggggcct 180
gaggcaagcc atggagtgag acccaggagc cggacacttc tcaggaaatg gcttttccca 240
acccccagcc cccacccggt ggttcttcct gttctgtgac tgtgtatagt gccaccacag 300
cttatggcat ctcattgagg acaaaaaaa 329

<210> 272
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 272
nggctgntaa cntcggaggt nacttcctgg actatcctgg agacccccctc cgcttccacg 60
nncatnatat cnctcatngc tgggcccntn angacacnat cccactccaa cacctgngng 120
atgctggncn cctnggaacc ancntcagaa ngaccctgnt cntntgtnnt ccgcaanctg 180
aagnnaangc gggntacacc tncntgcant ggnccacnct gcngggaact ntacacacct 240
acgggatgtg gctgcgccan gagccaagag cntttctgga tgattcccca gcctcttgnn 300
agggantcta caacattgct nnntaccttt ntccnncngc nnntnntgga ntacaggngn 360
tnntaacact acatcttttt tactgcnccn tncttggtgg g 401

<210> 273
<211> 401

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 273
cagcaccatg aagatcaaga tcatcgcacc cccagagcgc aagtactcgg tgtggatcgg 60
tggctccatc ctggcctcac tgtccacctt ccagcagatg tggattagca agcaggagta 120
cgacgagtcg ggcccctcca tcgtccaccg caaatgcttc taaacggact cagcagatgc 180
gtagcatttg ctgcatgggt taattgagaa tagaaatttg cccctggcaa atgcacacac 240
ctcatgctag cctcacgaaa ctggaataag ccttcgaaaa gaaattgtcc ttgaagcttg 300
tatctgatat cagcactgga ttgtagaact tgttgctgat tttgaccttg tattgaagtt 360
aactgttccc cttggtatta acgtgtcagg gctgagtgnt c 401

<210> 274
<211> 401
<212> DNA
<213> Homo sapien

<400> 274
ccacccacac ccaccgcgcc ctcgttcgcc tcttctccgg gagccagtcc gcgccaccgc 60
cgccgcccag gccatcgcca ccctccgcag ccatgtccac caggtccgtg tcctcgtcct 120
cctaccgcag gatgttcggc ggcccgggca ccgcgagccg gccgagctcc agccggagct 180
acgtgactac gtccacccgc acctacagcc tgggcagcgc gctgcgcccc agcaccagcc 240
gcagcctcta cgcctcgtcc ccgggcggcg tgtatgccac gcgctcctct gccgtgcgcc 300
tgcggagcag cgtgcccggg gtgcggctcc tgcaggactc ggtggacttc tcgctggccg 360
acgccatcaa caccgagttc aagaacaccc gcaccaacga g 401

<210> 275
<211> 401
<212> DNA
<213> Homo sapien

<400> 275
ccacttccac cactttgtgg agcagtgcct tcagcgcaac ccggatgcca ggtatccctg 60
ctggcctggg cctgggcttc gggagagcag agggtgctca ggagggtaag gccagggtgt 120
gaagggactt acctcccaaa ggttctgcag gggaatctgg agctacacac aggagggatc 180
agctcctggg tgtgtcagag gccagcctgg ggagctctgg ccactgcttc ccatgagctg 240
agggagaggg agaggggacc cgaggctgag gcataagtgg caggatttcg ggaagctggg 300
gacacggcag tgatgctgcg gtctctcctc ccctttccct ccaggcccag tgccagcacc 360
ctcctgaacc actctttctt caagcagatc aagcgacgtg c 401

<210> 276
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 276
tctgatattg ntacccttga gccacctaag ttagaagaaa ttggaaatca agaagttgtc 60
attgttgaag aagcacagag ttcagaagac tttaacatgg gctcttcctc tagcagccag 120
tatactttct gtcagccaga aactgtattt tcatctcagc ctagtgatga tgaatcaagt 180
agtgatgaaa ccagtaatca gcccagtcct gcctttagac gacgccgtgc taggaagaag 240
accgtttctg cttcagaatc tgaagaccgg ctagttggtg aacaagaaac tgaaccttct 300
aaggagttga gtaaacgtca gttcagtagt ggtctcaata agtgtgttat acttgctttg 360
gtgattgcaa tcagcatggg atttggccat ttctatggca c 401

<210> 277
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 277
aactttggca acatatctca gcaaaaacta cagctatgtt attcatgcca aaataaaagc 60
tgtgcagagg agtggctgca atgaggtcac aacggtggtg gatgtaaaag agatcttcaa 120
gtcctcatca cccatccctc gaactcaagt cccgctcatt acaaattctt cttgccagtg 180
tccacacatc ctgccccatc aagatgttct catcatgtgt tacgagnggc gctcaaggat 240
gatgcttctt gaaaattgct tagttgaaaa atggagagat cagcttagta aaagatccat 300
acagtgggaa gagaggctgc aggaacagcg ganaacagtt caggacaaga agaaaacagc 360
cgggcgcacc agtcgtagta atccccccaa accaaaggga a 401

<210> 278
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 278
aatgagtgtg agaccacaaa tgaatgccgg gaggatgaaa tgtgttggaa ttatcatggc 60
ggcttccgtt gttatccacg aaatccttgt caagatccct acattctaac accagagaac 120
cgatgtgttt gcccagtctc aaatgccatg tgccgagaac tgccccagtc aatagtctac 180
aaatacatga gcatccgatc tgataggtct gtgccatcag acatcttcca gatacaggcc 240
acaactattt atgccaacac catcaatact tttcggatta aatctggaaa tgaaaatgga 300
gagtctacct acgacaacaa ancccctgtaa gtgcaatgct tgtgctcgtg aagncattat 360
caggaccaag agaacatatc gtggacctgg agatgctgac a 401

<210> 279
<211> 401
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 279
aaattattgc ctctgataca tacctaagtn aacanaacat taatacctaa gtaaacataa 60
cattacttgg agggttgcag nttctaantg aaactgtatt tgaaactttt aagtatactt 120
taggaaacaa gcatgaacgg cagtctagaa taccagaaac atctacttgg gtagcttggn 180
gccattatcc tgtggaatct gatatgtctg gnagcatgtc attgatggga catgaagaca 240
tctttggaaa tgatgagatt atttcctgtg ttaaaaaaaa aaaaaatctt aaattcctac 300
aatgtgaaac tgaaactaat aattttgatc ctgatgtatg ggacagcgta tctgtaccag 360
gctctaaata acaaaagnta gggngacaag nacatgttcc t 401

<210> 280
<211> 326
<212> DNA
<213> Homo sapien

<400> 280
gaagtggaat tgtataattc aattcgataa ttgatctcat gggctttccc tggaggaaag 60
gtttttttg ttgttttttt tttaagaact tgaaacttgt aaactgagat gtctgtagct 120
tttttgccca tctgtagtgt atgtgaagat ttcaaaacct gagagcactt tttctttgtt 180
tagaattatg agaaaggcac tagatgactt taggatttgc atttttccct ttattgcctc 240
atttcttgtg acgccttgtt ggggagggaa atctgtttat tttttcctac aaataaaaag 300
ctaagattct atatcgcaaa aaaaaa 326

<210> 281
<211> 374
<212> DNA
<213> Homo sapien

<400> 281
caacgcgttt gcaaatattc ccctggtagc ctacttcctt acccccgaat attggtaaga 60
tcgagcaatg gcttcaggac atgggttctc ttctcctgtg atcattcaag tgctcactgc 120
atgaagactg gcttgtctca gtgtttcaac ctcaccaggg ctgtctcttg gtccacacct 180
cgctccctgt tagtgccgta tgacagcccc catcaaatga ccttggccaa gtcacggttt 240
ctctgtggtc aaggttggtt ggctgattgg tggaaagtag ggtggaccaa aggaggccac 300
gtgagcagtc agcaccagtt ctgcaccagc agcgcctccg tcctagtggg tgttcctgtt 360
tctcctggcc ctgg 374

<210> 282
<211> 404
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(404)
<223> n = A,T,C or G

<400> 282
agtgtggtgg aattcccgca tcctanncgc cgactcacac aaggcagagt ngccatggag 60
aaaattccag tgtcagcatt cttgctcctt gtggccctct cctacactct ggccagagat 120
accacagtca aacctgnagc caaaaaggac acaaaggact ctcgacccaa actgccccan 180

accctctcca gaggttgggg tgaccaactc atctggactc anacatatga agaagctcta 240
tataaatcca agacaagcaa caaacccttg atgattattc atcacttgga tgagtgccca 300
cacagtcaag ctttaaagaa agtgtttgct gaaaataaag aaatccagaa attggcagag 360
cagtttgtcc tcctcaatct ggtttatgaa acaactgaca aaca 404

<210> 283
<211> 184
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(184)
<223> n = A,T,C or G

<400> 283
agtgtggtgg aattcacttg cttaanttgt gggcaaaaga gaaaaagaag gattgatcag 60
agcattgtgc aatacagttt cattaactcc ttccctcgct cccccaaaaa tttgaatttt 120
tttttcaaca ctcttacacc tgttatggaa aatgtcaacc tttgtaagaa aaccaaaata 180
aaaa 184

<210> 284
<211> 421
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(421)
<223> n = A,T,C or G

<400> 284
ctattaatcc tgccacaata tttttaatta cgtacaaaga tctgacatgt cacccaggga 60
cccatttcac ccactgctct gtttggccgc cagtcttttg tctctctctt cagcaatggt 120
gaggcggata ccctttcctc ggggaanana aatccatggt ttgttgccct tgccaataac 180
aaaaatgttg gaaagtcgag tggcaaagct gttgccattg gcatctttca cgtgaaccac 240
gtcaaaagat ccagggtgcc tctctctgtt ggtgatcaca ccaattcttc ctaggttagc 300
acctccagtc accatacaca ggttaccagt gtcgaacttg atgaaatcag taatcttgcc 360
agtctctaaa tcaatctgaa tggtatcatt caccttgatg aggggatcgg ggtagcggat 420
g 421

<210> 285
<211> 361
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(361)
<223> n = A,T,C or G

<400> 285
ctgggtggta actctttatt tcattgtccg gaanaaagat gggagtggga acagggtgga 60
cactgtgcag gcttcagctt ccactccggg caggattcag gctatctggg accgcaggga 120

ctgccaggtg cacagccctg gctcccgagg caggcaggca aggtgacggg actggaagcc 180
cttttcanag ccttggagga gctggtccgt ccacaagcaa tgagtgccac tctgcagttt 240
gcaggggatg gataaacagg gaaacactgt gcattcctca cagccaacag tgtaggtctt 300
ggtgaagccc cggcgctgag ctaagctcag gctgttccag ggagccacga aactgcaggt 360
a 361

<210> 286
<211> 336
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(336)
<223> n = A,T,C or G

<400> 286
tttgagtggc agcgccttta tttgtggggg ccttcaaggn agggtcgtgg ggggcagcgg 60
ggaggaanag ccganaaact gtgtgaccgg ggcctcaggt ggtgggcatt gggggctcct 120
cttgcanatg cccattggca tcaccggtgc agccattggt ggcagcgggt accggtcctt 180
tcttgttcaa catagggtag gtggcagcca cgggtccaac tcgcttgagg ctgggccctg 240
ggcgctccat tttgtgttcc angagcatgt ggttctgtgg cgggagcccc acgcaggccc 300
tgaggatgtt ctcgatgcag ctgcgctggc ggaaaa 336

<210> 287
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 287
tgggtaccaa atttntttat ttgaaggaat ggnacaaatc aaanaactta agnggatgtt 60
ttggtacaac ttatanaaaa ggnaaaggaa accccaacat gcatgcnctg ccttggngac 120
cagggaagtc accccacggc tatggggaaa ttancccgag gcttancttt cattatcact 180
gtctcccagg gngngcttgt caaaaanata ttccnccaag ccaaattcgg gcgctcccat 240
nttgcncaag ttggtcacgt ggtcacccaa ttctttgatg gctttcacct gctcattcag 300
g 301

<210> 288
<211> 358
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(358)
<223> n = A,T,C or G

<400> 288
aagtttttaa acttttttatt tgcatattaa aaaaattgng cattccaata attaaaatca 60

tttgaacaaa aaaaaaaatg gcactctgat taaactgcat tacagcctgc aggacacctt 120
gggccagctt ggttttactc tanatttcac tgtcgtccca ccccacttct tccaccccac 180
ttcttccttc accaacatgc aagttctttc cttccctgcc agccanatag atagacagat 240
gggaaaggca ggcgcggcct tcgttgtcag tagttctttg atgtgaaagg ggcagcacag 300
tcatttaaac ttgatccaac ctctttgcat cttacaaagt taaacagcta aaagaagt 358

<210> 289
<211> 462
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(462)
<223> n = A,T,C or G

<400> 289
ggcatcagaa atgctgttta tttctctgct gctcccaagc tggctggcct ttgcagagga 60
gcagacaaca gatgcatagt tgggganaaa gggaggacag gttccaggat agagggtgca 120
ggctgaggga ggaagggtaa naggaaggaa ggccatcctg gatccccaca tttcagtctc 180
anatgaggac aaagggactc ccaagccccc aaatcatcan aaaacaccaa ggagcaggag 240
gagcttgagc aggccccagg gagcctcana gccataccag ccactgtcta cttcccatcc 300
tcctctccca ttccctgtct gcttcanacc acctcccagc taagccccag ctccattccc 360
ccaatcctgg cccttgccag cttgacagtc acagtgcctg gaattccacc actgaggctt 420
ctcccagttg gattaggacg tcgccctgtt agcatgctgc cc 462

<210> 290
<211> 481
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

<400> 290
tactttccta aactttatta aagaaaaaag caataagcaa tggnggtaaa tctctanaac 60
atacccaatt ttctgggctt cctccccnga gaatgtgaca ttttgatttc caaacatgcc 120
anaagtgtat ggttcccaac tgtactaaag taggtganaa gctgaagtcc tcaagtgttc 180
atcttccaac ttttcccagt ctgtggtctg tctttggatc agcaataatt gcctgaacag 240
ctactatggc ttcgttgatt tttgtctgta gctctctgag ctcctctatg tgcagcaatc 300
gcanaatttg agcagcttca ttaanaactg catctcctgt gtcaaaacca anaatatgtt 360
tgtctaaagc aacaggtaag ccctcttttg tttgatttgc cttancaact gcatcctgtg 420
tcaggcgctc ctgaaccaaa atccgaattg ccttaagcat taccaggtaa tcatcatgac 480
g 481

<210> 291
<211> 381
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(381)
<223> n = A,T,C or G

<400> 291
tcatagtaat gtaaaaccat ttgtttaatt ctaaatcaaa tcactttcac aacagtgaaa 60
attagtgact ggttaaggng tgccactgta catatcatca ttttctgact ggggtcagga 120
cctggtccta gtccacaagg gtggcaggag gagggtggag gctaanaaca cagaaaacac 180
acaaaanaaa ggaaagctgc cttggcanaa ggatgaggng gtgagcttgc cgaaggatgg 240
tgggaagggg gctccctgtt ggggccgagc caggagtccc aagtcagctc tcctgcctta 300
cttagctcct ggcanagggt gagtggggac ctacgaggtt caaaatcaaa tggcatttgg 360
ccagcctggc tttactaaca g 381

<210> 292
<211> 371
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(371)
<223> n = A,T,C or G

<400> 292
gaaaaaataa tccgtttaat tgaaaaacct gnaggatact attccactcc cccanatgag 60
gaggctgagg anaccaaacc cctacatcac ctcgtagcca cttctgatac tcttcacgag 120
gcagcaggca aagacaattc ccaaaacctc nacaaaagca attccaaggg ctgctgcagc 180
taccaccanc acatttttcc tcagccagcc cccaatcttc tccacacagc cctccttatg 240
gatcgccttc tcgttgaaat taatcccaca gcccacagta acattaatgc ancaggagtc 300
ggggactcgg ttcttcgaca tggaagggat tttctcccaa tctgtgtagt tagcagcccc 360
acagcactta a 371

<210> 293
<211> 361
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(361)
<223> n = A,T,C or G

<400> 293
gatttaaaag aaaacacttt attgttcagc aattaaaagt tagccaaata tgtatttttc 60
tccataattt attgngatgt tatcaacatc aagtaaaatg ctcattttca tcatttgctt 120
ctgttcatgt tttcttgaac acgtcttcaa ttttccttcc aaaatgctgc atgccacact 180
tgaggtaacg aagcanaagt atttttaaac atgacagcta anaacattca tctacagcaa 240
cctatatgct caatacatgc cgcgtgatcc tagtagtttt ttcacaacct tctacaagtt 300
tttggaaaac atctgttatg atgactttca tacaccttca cctcaaaggc tttcttgcac 360
c 361

<210> 294
<211> 391
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(391)
<223> n = A,T,C or G

<400> 294
tattttaaag tttaattatg attcanaaaa aatcgagcga ataactttct ctgaaaaaat 60
atattgactc tgtatanacc acagttattg gggganaagg gctggtaggt taaattatcc 120
tatttttat tctgaaaatg atattaatan aaagtcccgt ttccagtctg attataaaga 180
tacatatgcc caaaatggct ganaataaat acaacaggaa atgcaaaagc tgtaaagcta 240
agggcatgca ananaaaatc tcanaatacc caaagnggca acaaggaacg tttggctgga 300
atttgaagtt atttcagtca tctttgtctt tggctccatg tttcaggatg cgtgtgaact 360
cgatgtaatt gaaattcccc ttttttatcaa t 391

<210> 295
<211> 343
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(343)
<223> n = A,T,C or G

<400> 295
ttcttttgtt ttattgataa cagaaactgt gcataattac agatttgatg aggaatctgc 60
aaataataaa gaatgtgtct actgccagca aaatacaatt attccatgcc ctctcaacat 120
acaaatatag agttcttcac accanatggc tctggtgtaa caaagccatt ttanatgttt 180
aattgtgctt ctacaaaacc ttcanagcat gaggtagttt cttttaccta cnatattttc 240
cacatttcca ttattacact tttagtgagc taaaatcctt ttaacatagc ctgcggatga 300
tctttcacaa aagccaagcc tcatttacaa agggtttatt tct 343

<210> 296
<211> 241
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 296
ttcttggata ttggttgttt ttgtgaaaaa gtttttgttt ttcttctcag tcaactgaat 60
tatttctcta ctttgccctc ctgatgccca catgananaa cttaanataa tttctaacag 120
cttccacttt ggaaaaaaaa aaaacctgtt ttcctcatgg aaccccagga gttgaaagtg 180
gatanatcgc tctcaaaatc taaggctctg ttcagcttta cattatgtta cctgacgttt 240
t 241

<210> 297
<211> 391
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(391)
<223> n = A,T,C or G

<400> 297
gttgtggctg anaatgctgg agatgctcag ttctctccct cacaaggtag gccacaaatt 60
cttggtggtg ccctcacatc tggggtcttc aggcaccagc catgcctgcc gaggagtgct 120
gtcaggacan accatgtccg tgctaggccc aggcacagcc caaccactcc tcatccaagt 180
ctctcccagg tttctggtcc cgatgggcaa ggatgacccc tccagtggct ggtaccccac 240
catcccacta cccctcacat gctctcactc tccatcaggt ccccaatcct ggcttccctc 300
ttcacgaact ctcaaagaaa aggaaggata aaacctaaat aaaccagaca gaagcagctc 360
tggaaaagta caaaaagaca gccagaggtg t 391

<210> 298
<211> 321
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(321)
<223> n = A,T,C or G

<400> 298
caagccaaac tgtntccagc tttattaaan atactttcca taaacaatca tggtatttca 60
ggcaggacat gggcanacaa tcgttaacag tatacaacaa ctttcaaact cccttnttca 120
atggactacc aaaaatcaaa aagccactat aaaacccaat gaagtcttca tctgatgctc 180
tgaacaggga aagtttaaag ngagggttga catttcacat ttagcatgtt gtttaacaac 240
ttttcacaag ccgaccctga ctttcaggaa gtgaaatgaa aatggcanaa tttatctgaa 300
natccacaat ctaaaaatgg a 321

<210> 299
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 299
tatcataaag agtgttgaag tttatttatt atagcaccat tgagacattt tgaaattgga 60
attggtaaaa aaataaaaca aaaagcattt gaattgtatt tggnggaaca gcaaaaaaag 120
agaagtatca tttttctttg tcaaattata ctgtttccaa acattttgga aataaataac 180
tggaattttg tcggtcactt gcactggttg acaagattag aacaagagga acacatatgg 240
agttaaattt tttttgttgg gatttcanat agagtttggt ttataaaaag caaacagggc 300
caacgtccac accaaattct tgatcaggac caccaatgtc atagggngca atatctacaa 360
taggtagtct cacagccttg cgtgttcgat attcaaagac t 401

<210> 300
<211> 188

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(188)
<223> n = A,T,C or G

<400> 300
tgaatgcttt gtcatattaa gaaagttaaa gtgcaataat gtttgaanac aataagtggt 60
ggtgtatctt gtttctaata agataaactt ttttgtcttt gctttatctt attagggagt 120
tgtatgtcag tgtataaaac atactgtgtg gtataacagg cttaataaat tctttaaaag 180
gaaaaaaa 188

<210> 301
<211> 291
<212> DNA
<213> Homo sapien

<400> 301
aagattttgt tttattttat tatggctaga aagacactgt tatagccaaa atcggcaatg 60
acactaaaga aatcctctgt gcttttcaat atgcaaatat atttcttcca agagttgccc 120
tggtgtgact tcaagagttc atgttaactt cttttctgga aacttccttt tcttagttgt 180
tgtattcttg aagagcctgg gccatgaaga gcttgcctaa gttttgggca gtgaactcct 240
tgatgttctg gcagtaagtg tttatctggc ctgcaatgag cagcgagtcc a 291

<210> 302
<211> 341
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(341)
<223> n = A,T,C or G

<400> 302
tgatttttca taattttatt aaatnatcac tgggaaaact aatggttcgc gtatcacaca 60
attacactac aatctgatag gagtggtaaa accagccaat ggaatccagg taaagtacaa 120
aaacgccacc ttttattgtc ctgtcttatt tctcgggaag gagggttcta ctttacacat 180
ttcatgagcc agcagtggac ttgagttaca atgtgtaggt tccttgtggt tatagctgca 240
gaagaagcca tcaaattctt gaggacttga catctctcgg aaagaagcaa actagtggat 300
cccccgggct gcaggaattc gatatcaagc ttatcgatac c 341

<210> 303
<211> 361
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(361)
<223> n = A,T,C or G

<400> 303
tgcagacagt aaatnaattt tatttgngtt cacagaacat actaggcgat ctcgacagtc 60
gctccgtgac agcccaccaa cccccaaccc tntacctcgc agccacccta aaggcgactt 120
caanaanatg gaaggatctc acggatctca ttcctaatgg tccgccgaag tctcacacag 180
tanacagacg gagttganat gctggaggat gcagtcacct cctaaactta cgacccacca 240
ccanacttca tcccagccgg gacgtcctcc cccacccgag tcctccccat ttcttctcct 300
actttgccgc agttccaggn gtcctgcttc caccagtccc acaaagctca ataaatacca 360
a 361

<210> 304
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 304
ctctttacaa cagcctttat ttncggccct tgatcctgct cggatgctgg tggaggccct 60
tagctccgcc cgccaggctc tgtgccgcct ccccgcaggc gcanattcat gaacacggtg 120
ctcaggggct tgaggccgta ctcccccagc gggagctggt cctccagggg cttcccctcg 180
aaggtcagcc anaacaggtc gtcctgcaca ccctccagcc cgctcacttg ctgcttcagg 240
tgggccacgg tctgcgtcag ccgcacctcg taggtgctgc tgcggccctt gttattcctc 300
a 301

<210> 305
<211> 331
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(331)
<223> n = A,T,C or G

<400> 305
ganaggctag taacatcagt tttattgggt tggggnggca accatagcct ggctgggggn 60
ggggctggcc ctcacaggtt gttgagttcc agcagggtct ggtccaaggt ctggtgaatc 120
tcgacgttct cctccttggc actggccaag gtctcttcta ggtcatcgat ggttttctcc 180
aactttgcca canacctctc ggcaaactct gctcgggtct cancctcctt cagcttctcc 240
tccaacagtt tgatctcctc ttcatattta tcttctttgg gggaatactc ctcctctgag 300
gccatcaggg acttgagggc ctggtccatg g 331

<210> 306
<211> 457
<212> DNA
<213> Homo sapien

<400> 306
aatatgtaaa ggtaataact tttattatat taaagacaat gcaaacgaaa aacagaattg 60
agcagtgcaa aatttaaagg actgttttgt tctcaaagtt gcaagtttca aagccaaaag 120
aattatatgt atcaaatata taagtaaaaa aaagttagac tttcaagcct gtaatcccag 180

cactttggga ggctgaggca ggtggatcac taacattaaa aagacaacat tagattttgt 240
cgatttatag caattttata aatatataac tttgtcactt ggatcctgaa gcaaaataat 300
aaagtgaatt tgggattttt gtacttggta aaaagtttaa caccctaaat tcacaactag 360
tggatccccc gggctgcagg aattcgatat caagcttatc gataccgtcg acctcgaggg 420
ggggcccggt acccaattcg ccctatagtg agtcgta 457

<210> 307
<211> 491
<212> DNA
<213> Homo sapien

<400> 307
gtgcttggac ggaacccggc gctcgttccc caccccggcc ggccgcccat agccagccct 60
ccgtcacctc ttcaccgcac cctcggactg ccccaaggcc cccgccgccg ctccagcgcc 120
gcgcagccac cgccgccgcc gccgcctctc cttagtcgcc gccatgacga ccgcgtccac 180
ctcgcaggtg cgccagaact accaccagga ctcagaggcc gccatcaacc gccagatcaa 240
cctggagctc tacgcctcct acgtttacct gtccatgtct tactactttg accgcgatga 300
tgtggctttg aagaactttg ccaaatactt tcttcaccaa tctcatgagg agagggaaca 360
tgctgagaaa ctgatgaagc tgcagaacca acgaggtggc cgaatcttcc ttcaggatat 420
caagaaacca gactgtgatg actgggagag cgggctgaat gcaatggagt gtgcattaca 480
tttggaaaaa a 491

<210> 308
<211> 421
<212> DNA
<213> Homo sapien

<400> 308
ctcagcgctt cttctttctt ggtttgatcc tgactgctgt catggcgtgc cctctggaga 60
aggccctgga tgtgatggtg tccaccttcc acaagtactc gggcaaagag ggtgacaagt 120
tcaagctcaa caagtcagaa ctaaaggagc tgctgacccg ggagctgccc agcttcttgg 180
ggaaaaggac agatgaagct gctttccaga agctgatgag caacttggac agcaacaggg 240
acaacgaggt ggacttccaa gagtactgtg tcttcctgtc ctgcatcgcc atgatgtgta 300
acgaattctt tgaaggcttc ccagataagc agcccaggaa gaaatgaaaa ctcctctgat 360
gtggttgggg ggtctgccag ctggggccct ccctgtcgcc agtgggcact ttttttttc 420
c 421

<210> 309
<211> 321
<212> DNA
<213> Homo sapien

<400> 309
accaaatggc ggatgacgcc ggtgcagcgg gggggcccgg gggccctggt ggccctggga 60
tggggaaccg cggtggcttc cgcggaggtt tcggcagtgg catccggggc cggggtcgcg 120
gccgtggacg gggccggggc cgaggccgcg gagctcgcgg aggcaaggcc gaggataagg 180
agtggatgcc cgtcaccaag ttgggccgct tggtcaagga catgaagatc aagtccctgg 240
aggagatcta tctcttctcc ctgcccatta aggaatcaga gatcattgat ttcttcctgg 300
gggcctctct caaggatgag g 321

<210> 310
<211> 381
<212> DNA
<213> Homo sapien

<400> 310
ttaaccagcc atattggctc aataaatagc ttcggtaagg agttaatttc cttctagaaa 60
tcagtgccta tttttcctgg aaactcaatt ttaaatagtc caattccatc tgaagccaag 120
ctgttgtcat tttcattcgg tgacattctc tcccatgaca cccagaaggg gcagaagaac 180
cacatttttc atttatagat gtttgcatcc tttgtattaa aattattttg aaggggttgc 240
ctcattggat ggctttttt ttttttcctcc agggagaagg ggagaaatgt acttggaaat 300
taatgtatgt ttacatctct ttgcaaattc ctgtacatag agatatattt tttaagtgtg 360
aatgtaacaa catactgtga a 381

<210> 311
<211> 538
<212> DNA
<213> Homo sapien

<400> 311
tttgaattta caccaagaac ttctcaataa aagaaaatca tgaatgctcc acaatttcaa 60
cataccacaa gagaagttaa tttcttaaca ttgtgttcta tgattatttg taagaccttc 120
accaagttct gatatctttt aaagacatag ttcaaaattg cttttgaaaa tctgtattct 180
tgaaaatatc cttgttgtgt attaggtttt taaataccag ctaaaggatt acctcactga 240
gtcatcagta ccctcctatt cagctcccca agatgatgtg tttttgctta ccctaagaga 300
ggttttcttc ttatttttag ataattcaag tgcttagata aattatgttt tctttaagtg 360
tttatggtaa actcttttaa agaaaattta atatgttata gctgaatctt tttggtaact 420
ttaaatcttt atcatagact ctgtacatat gttcaaatta gctgcttgcc tgatgtgtgt 480
atcatcggtg ggatgacaga acaaacatat ttatgatcat gaataatgtg ctttgtaa 538

<210> 312
<211> 176
<212> DNA
<213> Homo sapien

<400> 312
ggaggagcag ctgagagata gggtcagtga atgcggttca gcctgctacc tctcctgtct 60
tcatagaacc attgccttag aattattgta tgacacgttt tttgttggtt aagctgtaag 120
gttttgttct ttgtgaacat gggtattttg aggggagggt ggagggagta gggaag 176

<210> 313
<211> 396
<212> DNA
<213> Homo sapien

<400> 313
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tggcgctccc atggctcttg caacatctcc ccttcgtttt tgaggggtc atgccggggg 120
agccaccagc ccctcactgg gttcggagga gagtcaggaa gggccaagca cgacaaagca 180
gaaacatcgg atttggggaa cgcgtgtcaa tcccttgtgc cgcagggctg ggcgggagag 240
actgttctgt tccttgtgta actgtgttgc tgaaagacta cctcgttctt gtcttgatgt 300
gtcaccgggg caactgcctg ggggcgggga tgggggcagg gtggaagcgg ctccccattt 360
tataccaaag gtgctacatc tatgtgatgg gtgggg 396

<210> 314
<211> 311
<212> DNA
<213> Homo sapien

<400> 314
cctcaacatc ctcagagagg actggaagcc agtccttacg ataaactcca taatttatgg 60
cctgcagtat ctcttcttgg agcccaaccc cgaggaccca ctgaacaagg aggccgcaga 120
ggtcctgcag aacaaccggc ggctgtttga gcagaacgtg cagcgctcca tgcggggtgg 180
ctacatcggc tccacctact ttgagcgctg cctgaaatag ggttggcgca tacccacccc 240
cgccacggcc acaagccctg gcatcccctg caaatattta ttgggggcca tgggtagggg 300
tttgggggggc g 311

<210> 315
<211> 336
<212> DNA
<213> Homo sapien

<400> 315
tttagaacat ggttatcatc caagactact ctaccctgca acattgaact cccaagagca 60
aatccacatt cctcttgagt tctgcagctt ctgtgtaaat agggcagctg tcgtctatgc 120
cgtagaatca catgatctga ggaccattca tggaagctgc taaatagcct agtctgggga 180
gtcttccata aagttttgca tggagcaaac aaacaggatt aaactaggtt tggttccttc 240
agccctctaa aagcataggg cttagcctgc aggcttcctt gggctttctc tgtgtgtgta 300
gttttgtaaa cactatagca tctgttaaga tccagt 336

<210> 316
<211> 436
<212> DNA
<213> Homo sapien

<400> 316
aacatggtct gcgtgcctta agagagacgc ttcctgcaga acaggacctg actacaaaga 60
atgtttccat tggaattgtt ggtaaagact tggagtttac aatctatgat gatgatgatg 120
tgtctccatt cctggaaggt cttgaagaaa gaccacagag aaaggcacag cctgctcaac 180
ctgctgatga acctgcagaa aaggctgatg aaccaatgga acattaagtg ataagccagt 240
ctatatatgt attatcaaat atgtaagaat acaggcacca catactgatg acaataatct 300
atactttgaa ccaaaagttg cagagtggtg gaatgctatg ttttaggaat cagtccagat 360
gtgagttttt tccaagcaac ctcactgaaa cctatataat ggaatacatt tttctttgaa 420
agggtctgta taatca 436

<210> 317
<211> 196
<212> DNA
<213> Homo sapien

<400> 317
tattccttgt gaagatgata tactattttt gttaagcgtg tctgtattta tgtgtgagga 60
gctgctggct tgcagtgcgc gtgcacgtgg agagctggtg cccggagatt ggacggcctg 120
atgctccctc ccctgccctg gtccagggaa gctggccgag ggtcctggct cctgaggggc 180
atctgccccc ccccca 196

<210> 318
<211> 381
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(381)
<223> n = A,T,C or G

<400> 318
gacgcttnng ccgtaacgat gatcggagac atcctgctgt tcgggacgtt gctgatgaat 60
gccggggcgg tgctgaactt taagctgaaa aagaaggaca cncagggctt tggggaggag 120
tncagggagc ccaacacagg tgacaacatc cgggaattct tgctgancct cagatacttt 180
cnaatcttca tcncgctgtg gaacatcttc atgatgttct gcatgattgt gctgntcggc 240
tcttgaatcc cancgatgaa accannaact cactttcccg ggatgccgan tctccattcc 300
tccattcctg atgacttcaa naatgttttt gaccaaaaaa ccgacaacct tcccagaaag 360
tccaagctcg tggtgggngg a 381

<210> 319
<211> 506
<212> DNA
<213> Homo sapien

<400> 319
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tttgtaaata cctttgttat aattgatagg atacatcttg gacatggaat tgttaagcca 120
cctctgagca gtgtatgtca ggacttgttc attaggttgg cagcagaggg gcagaaggaa 180
ttatacaggt agagatgtat gcagatgtgt ccatatatgt ccatatttac attttgatag 240
ccattgatgt atgcatctct tggctgtact ataagaacac attaattcaa tggaaataca 300
ctttgctaat attttaatgg tatagatctg ctaatgaatt ctcttaaaaa catactgtat 360
tctgttgctg tgtgtttcat tttaaattga gcattaaggg aatgcagcat ttaaatcaga 420
actctgccaa tgcttttatc tagaggcgtg ttgccatttt tgtcttatat gaaatttctg 480
tcccaagaaa ggcaggatta catctt 506

<210> 320
<211> 351
<212> DNA
<213> Homo sapien

<400> 320
ctgacctgca ggacgaaacc atgaagagcc tgatccttct tgccatcctg gccgccttag 60
cggtagtaac tttgtgttat gaatcacatg aaagcatgga atcttatgaa cttaatccct 120
tcattaacag gagaaatgca aataccttca tatcccctca gcagagatgg agagctaaag 180
tccaagagag gatccgagaa cgctctaagc ctgtccacga gctcaatagg gaagcctgtg 240
atgactacag actttgcgaa cgctacgcca tggtttatgg atacaatgct gcctataatc 300
gctacttcag gaagcgccga gggaccaaat gagactgagg gaagaaaaaa a 351

<210> 321
<211> 421
<212> DNA
<213> Homo sapien

<400> 321
ctcggaggcg ttcagctgct tcaagatgaa gctgaacatc tccttcccag ccactggctg 60
ccagaaactc attgaagtgg acgatgaacg caaacttcgt actttctatg agaagcgtat 120
ggccacagaa gttgctgctg acgctctggg tgaagaatgg aagggttatg tggtccgaat 180
cagtggtggg aacgacaaac aaggtttccc catgaagcag ggtgtcttga cccatggccg 240
tgtccgcctg ctactgagta aggggcattc ctgttacaga ccaaggagaa ctggagaaag 300
aaagagaaaa tcagttcgtg gttgcattgt ggatgcaaat ctgagcgttc tcaacttggt 360

tattgtaaaa aaaggagaga aggatattcc tggactgact gatactacag tgcctcgccg 420
c 421

<210> 322
<211> 521
<212> DNA
<213> Homo sapien

<400> 322
agcagctctc ctgccacagc tcctcacccc ctgaaaatgt tcgcctgctc caagtttgtc 60
tccactccct ccttggtcaa gagcacctca cagctgctga gccgtccgct atctgcagtg 120
gtgctgaaac gaccggagat actgacagat gagagcctca gcagcttggc agtctcatgt 180
ccccttacct cacttgtctc tagccgcagc ttccaaacca gcgccatttc aagggacatc 240
gacacagcag ccaagttcat tggagctggg gctgccacag ttggggtggc tggttctggg 300
gctgggattg gaactgtgtt tgggagcctc atcattggtt atgccaggaa cccttctctg 360
aagcaacagc tcttctccta cgccattctg ggctttgccc tctcggaggc catggggctc 420
ttttgtctga tggtagcctt tctcatcctc tttgccatgt gaaggagccg tctccacctc 480
ccatagttct cccgcgtctg gttggccccg tgtgttcctt t 521

<210> 323
<211> 435
<212> DNA
<213> Homo sapien

<400> 323
ccgaggtcgc acgcgtgaga cttctccgcc gcagacgccg ccgcgatgcg ctacgtcgcc 60
tcctacctgc tggctgccct agggggcaac tcctccccca gcgccaagga catcaagaag 120
atcttggaca gcgtgggtat cgaggcggac gacgaccggc tcaacaaggt tatcagtgag 180
ctgaatggaa aaaacattga agacgtcatt gcccagggta ttggcaagct tgccagtgta 240
cctgctggtg gggctgtagc cgtctctgct gccccaggct ctgcagcccc tgctgctggt 300
tctgcccctg ctgcagcaga ggagaagaaa gatgagaaga aggaggagtc tgaagagtca 360
gatgatgaca tgggatttgg ccttttttgat taaattcctg ctcccctgca aataaagcct 420
ttttacacat ctcaa 435

<210> 324
<211> 521
<212> DNA
<213> Homo sapien

<400> 324
aggagatcga ctttcggtgc ccgcaagacc agggctggaa cgccgagatc acgctgcaga 60
tggtgcagta caagaatcgt caggccatcc tggcggtcaa atccacgcgg cagaagcagc 120
agcacctggt ccagcagcag ccccccctcgc agccgcagcc gcagccgcag ctccagcccc 180
aaccccagcc tcagcctcag ccgcaacccc agccccaatc acaaccccag cctcagcccc 240
aacccaagcc tcagccccag cagctccacc cgtatccgca tccacatcca catccacact 300
ctcatcctca ctcgcaccca caccctcacc cgcacccgca tccgcaccaa ataccgcacc 360
cacacccaca gccgcactcg cagccgcacg ggcaccggct tctccgcagc acctccaact 420
ctgcctgaaa ggggcagctc ccgggcaaga caaggttttg aggacttgag gaagtgggac 480
gagcacattt ctattgtctt cacttggatc aaaagcaaaa c 521

<210> 325
<211> 451
<212> DNA
<213> Homo sapien

<400> 325
attttcattt ccattaacct ggaagctttc atgaatattc tcttctttta aaacatttta 60
acattattta aacagaaaaa gatgggctct ttctggttag ttgttacatg atagcagaga 120
tatttttact tagattactt tgggaatgag agattgttgt cttgaactct ggcactgtac 180
agtgaatgtg tctgtagttg tgttagtttg cattaagcat gtataacatt caagtatgtc 240
atccaaataa gaggcatata cattgaattg tttttaatcc tctgacaagt tgactcttcg 300
acccccaccc ccacccaaga cattttaata gtaaatagag agagagagaa gagttaatga 360
acatgaggta gtgttccact ggcaggatga cttttcaata gctcaaatca atttcagtgc 420
ctttatcact tgaattatta acttaatttg a 451

<210> 326
<211> 421
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(421)
<223> n = A,T,C or G

<400> 326
cgcggtcgta agggctgagg atttttggtc cgcacgctcc tgctcctgac tcaccgctgt 60
tcgctctcgc cgaggaacaa gtcggtcagg aagcccgcgc gcaacagcca tggcttttaa 120
ggataccgga aaaacacccg tggagccgga ggtggcaatt caccgaattc gaatcaccct 180
aacaagccgc aacgtaaaat ccttggaaaa ggtgtgtgct gacttgataa gaggcgcaaa 240
agaaaagaat ctcaaagtga aaggaccagt tcgaatgcct accaagactt tgagantcac 300
tacaagaaaa actccttgtg gtgaaggttc taagacgtgg gatcgtttcc agatgagaat 360
tcacaagcga ctcattgact tgcacagtcc ttctgagatt gttaagcaga ttacttccat 420
c 421

<210> 327
<211> 456
<212> DNA
<213> Homo sapien

<400> 327
atcttgacga ggctgcggtg tctgctgcta ttctccgagc ttcgcaatgc cgcctaagga 60
cgacaagaag aagaaggacg ctggaaagtc ggccaagaaa gacaaagacc cagtgaacaa 120
atccgggggc aaggccaaaa agaagaagtg gtccaaaggc aaagttcggg acaagctcaa 180
taacttagtc ttgtttgaca aagctaccta tgataaactc tgtaaggaag ttcccaacta 240
taaacttata accccagctg tggtctctga gagactgaag attcgaggct ccctggccag 300
ggcagcccct caggagctcc ttagtaaagg acttatcaaa ctggtttcaa agcacagagc 360
tcaagtaatt tacaccagaa ataccaaggg tggagatgct ccagctgctg gtgaagatgc 420
atgaataggt ccaaccagct gtacatttgg aaaaat 456

<210> 328
<211> 471
<212> DNA
<213> Homo sapien

<400> 328
gtggaagtga catcgtcttt aaaccctgcg tggcaatccc tgacgcaccg ccgtgatgcc 60
cagggaagac agggcgacct ggaagtccaa ctacttcctt aagatcatcc aactattgga 120

tgattatccg aaatgtttca ttgtgggagc agacaatgtg ggctccaagc agatgcagca 180
gatccgcatg tcccttcgcg ggaaggctgt ggtgctgatg ggcaagaaca ccatgatgcg 240
caaggccatc cgagggcacc tggaaaacaa cccagctctg gagaaactgc tgcctcatat 300
ccgggggaat gtgggctttg tgttcaccaa ggaggacctc actgagatca gggacatgtt 360
gctggccaat aaggtgccag ctgctgcccg tgctggtgcc attgccccat gtgaagtcac 420
tgtgccagcc cagaacactg gtctcgggcc cgagaagacc tccttttttcc a 471

<210> 329
<211> 278
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(278)
<223> n = A,T,C or G

<400> 329
gtttaaactt aagcttggta ccgagctcgg atccactagt ccagtgtggt ggaattctag 60
aaattgagat gccccccccag gccagcaaat gttccttttt gttcaaagtc tatttttatt 120
ccttgatatt tttcttttttt ttttttttttt ttgnggatgg ggacttgtga atttttctaa 180
aggtgctatt taacatggga gganagcgtg tgcggctcca gcccagcccg ctgctcactt 240
tccaccctct ctccacctgc ctctggcttc tcaggcct 278

<210> 330
<211> 338
<212> DNA
<213> Homo sapien

<400> 330
ctcaggcttc aacatcgaat acgccgcagg ccccttcgcc ctattcttca tagccgaata 60
cacaaacatt attataataa acaccctcac cactacaatc ttcctaggaa caacatatga 120
cgcactctcc cctgaactct acacaacata ttttgtcacc aagaccctac ttctaacctc 180
cctgttctta tgaattcgaa cagcataccc ccgattccgc tacgaccaac tcatacacct 240
cctatgaaaa aacttcctac cactcaccct agcattactt atatgatatg tctccatacc 300
cattacaatc tccagcattc cccctcaaac ctaaaaaa 338

<210> 331
<211> 2820
<212> DNA
<213> Homo sapiens

<400> 331
tggcaaaatc ctggagccag aagaaaggac agcagcattg atcaatctta cagctaacat 60
gttgtacctg gaaaacaatg cccagactca atttagtgag ccacagtaca cgaacctggg 120
gctcctgaac agcatggacc agcagattcg gaacggctcc tcgtccacca gtccctataa 180
cacagaccac gcgcagaaca gcgtcacggc gccctcgccc tacgcacagc ccagccccac 240
cttcgatgct ctctctccat cacccgccat cccctccaac accgactacc caggcccgca 300
cagttccgac gtgtccttcc agcagtcgag caccgccaag tcggccacct ggacgtattc 360
cactgaactg aagaaactct actgccaaat tgcaaagaca tgccccatcc agatcaaggt 420
gatgacccca cctcctcagg gagctgttat ccgcgccatg cctgtctaca aaaaagctga 480
gcacgtcacg gaggtggtga agcggtgccc caaccatgag ctgagccgtg agttcaacga 540
gggacagatt gcccctccta gtcatttgat tcgagtagag gggaacagcc atgcccagta 600

tgtagaagat cccatcacag gaagacagag tgtgctggta ccttatgagc caccccaggt 660
tggcactgaa ttcacgacag tcttgtacaa tttcatgtgt aacagcagtt gtgttggagg 720
gatgaaccgc cgtccaattt taatcattgt tactctggaa accagagatg ggcaagtcct 780
gggccgacgc tgctttgagg cccggatctg tgcttgccca ggaagagaca ggaaggcgga 840
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gcgcccgttt cgtcagaaca cacatggtat ccagatgaca tccatcaaga aacgaagatc 960
cccagatgat gaactgttat acttaccagt gaggggccgt gagacttatg aaatgctgtt 1020
gaagatcaaa gagtccctgg aactcatgca gtaccttcct cagcacacaa ttgaaacgta 1080
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ccactgcaca cccccacctc cgtatcccac agattgcagc attgtcagtt tcttagcgag 1440
gttgggctgt tcatcatgtc tggactattt cacgacccag gggctgacca ccatctatca 1500
gattgagcat tactccatgg atgatctggc aagtctgaaa atccctgagc aatttcgaca 1560
tgcgatctgg aagggcatcc tggaccaccg gcagctccac gaattctcct ccccttctca 1620
tctcctgcgg accccaagca gtgcctctac agtcagtgtg ggctccagtg agacccgggg 1680
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agatgagtgg aatgacttca actttgacat ggatgctcgc cgcaataagc aacagcgcat 1800
caaagaggag ggggagtgag cctcaccatg tgagctcttc ctatccctct cctaactgcc 1860
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ctgccatggc taggtagaag tgagcaaaaa agagttgggt gtctccttaa gctgcagaga 2100
tttctcattg acttttataa agcatgttca cccttatagt ctaagactat atatataaat 2160
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ttaaatgaaa gaaaattgag ttgcacttat tgaccatttt ttaatttact tgttttggat 2280
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taccttatct tacaatgttg attgggaaaa catttgctgc ccattacaga ggtattaaaa 2760
ctaaatttca ctactagatt gactaactca aatacacatt tgctactgtt gtaagaattc 2820

<210> 332
<211> 2270
<212> DNA
<213> Homo sapiens

<400> 332
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acagtactgc cctgaccctt acatccagcg tttcgtagaa acccagctca tttctcttgg 120
aaagaaagtt attaccgatc caccatgtcc cagagcacac agacaaatga attcctcagt 180
ccagaggttt tccagcatat ctgggatttt ctggaacagc ctatatgttc agttcagccc 240
attgacttga actttgtgga tgaaccatca gaagatggtg cgacaaacaa gattgagatt 300
agcatggact gtatccgcat gcaggactcg gacctgagtg accccatgtg gccacagtac 360
acgaacctgg ggctcctgaa cagcatggac cagcagattc agaacggctc ctcgtccacc 420
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cccagctcca ccttcgatgc tctctctcca tcacccgcca tcccctccaa caccgactac 540

ccaggcccgc acagtttcga cgtgtccttc cagcagtcga gcaccgccaa gtcggccacc 600
tggacgtatt ccactgaact gaagaaactc tactgccaaa ttgcaaagac atgccccatc 660
cagatcaagg tgatgacccc acctcctcag ggagctgtta tccgcgccat gcctgtctac 720
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gaattcaacg agggacagat tgcccctcct agtcatttga ttcgagtaga ggggaacagc 840
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ccaccccagg ttggcactga attcacgaca gtcttgtaca atttcatgtg taacagcagt 960
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ttcttagcga ggttgggctg ttcatcatgt ctggactatt tcacgaccca ggggctgacc 1740
accatctatc agattgagca ttactccatg gatgatctgg caagtctgaa aatccctgag 1800
caatttcgac atgcgatctg gaagggcatc ctggaccacc ggcagctcca cgaattctcc 1860
tccccttctc atctcctgcg gaccccaagc agtgcctcta cagtcagtgt gggctccagt 1920
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tcctaactgc cagccccta aaagcactcc tgcttaatct tcaaagcctt ctccctagct 2160
cctccccttc ctcttgtctg atttcttagg ggaaggagaa gtaagaggct acctcttacc 2220
taacatctga cctggcatct aattctgatt ctggctttaa gccttcaaaa 2270

<210> 333
<211> 2816
<212> DNA
<213> Homo sapiens

<400> 333
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acagtactgc cctgaccctt acatccagcg tttcgtagaa acccagctca tttctcttgg 120
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Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
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Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Pro Thr Phe Asp Ala
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Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
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His Ser Ser Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
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Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
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Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
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Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
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Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
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Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn
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Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
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Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
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Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr
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Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His
                325                 330                 335

Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu
            340                 345                 350

Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser
        355                 360                 365

Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val
    370                 375                 380

Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr
385                 390                 395                 400

Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met
                405                 410                 415

Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro
            420                 425                 430

Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro
        435                 440                 445

Tyr Pro Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys
    450                 455                 460

Ser Ser Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr
465                 470                 475                 480
```

```
Gln Ile Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro
                485                 490                 495

Glu Gln Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln
            500                 505                 510

Leu His Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser
        515                 520                 525

Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val
    530                 535                 540

Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro
545                 550                 555                 560

Arg Asp Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn
                565                 570                 575

Lys Gln Gln Arg Ile Lys Glu Glu Gly Glu
            580                 585

<210> 339
<211> 641
<212> PRT
<213> Homo sapiens

<400> 339
Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe
                  5                  10                  15

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
             20                  25                  30

Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn
         35                  40                  45

Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
     50                  55                  60

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser
 65                  70                  75                  80

Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn
                 85                  90                  95

Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
            100                 105                 110

Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser
        115                 120                 125

Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln
    130                 135                 140
```

```
Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys
145                 150                 155                 160

Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val
                165                 170                 175

Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr
            180                 185                 190

Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His
        195                 200                 205

Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His
    210                 215                 220

Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro
225                 230                 235                 240

Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
                245                 250                 255

Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser
            260                 265                 270

Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu
        275                 280                 285

Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg
    290                 295                 300

Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile
305                 310                 315                 320

Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys
                325                 330                 335

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys
            340                 345                 350

Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly
        355                 360                 365

Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu
    370                 375                 380

Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln
385                 390                 395                 400

Gln Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser
                405                 410                 415

Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser
            420                 425                 430
```

Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg
435 440 445

Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile
450 455 460

Pro Met Met Gly Thr His Met Pro Met Ala Gly Asp Met Asn Gly Leu
465 470 475 480

Ser Pro Thr Gln Ala Leu Pro Pro Pro Leu Ser Met Pro Ser Thr Ser
485 490 495

His Cys Thr Pro Pro Pro Pro Tyr Pro Thr Asp Cys Ser Ile Val Gly
500 505 510

Phe Leu Ala Arg Leu Gly Cys Ser Ser Cys Leu Asp Tyr Phe Thr Thr
515 520 525

Gln Gly Leu Thr Thr Ile Tyr Gln Ile Glu His Tyr Ser Met Asp Asp
530 535 540

Leu Ala Ser Leu Lys Ile Pro Glu Gln Phe Arg His Ala Ile Trp Lys
545 550 555 560

Gly Ile Leu Asp His Arg Gln Leu His Glu Phe Ser Ser Pro Ser His
565 570 575

Leu Leu Arg Thr Pro Ser Ser Ala Ser Thr Val Ser Val Gly Ser Ser
580 585 590

Glu Thr Arg Gly Glu Arg Val Ile Asp Ala Val Arg Phe Thr Leu Arg
595 600 605

Gln Thr Ile Ser Phe Pro Pro Arg Asp Glu Trp Asn Asp Phe Asn Phe
610 615 620

Asp Met Asp Ala Arg Arg Asn Lys Gln Gln Arg Ile Lys Glu Glu Gly
625 630 635 640

Glu

<210> 340
<211> 448
<212> PRT
<213> Homo sapiens

<400> 340
Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe
5 10 15

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
20 25 30

```
Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn
          35                  40                  45

Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
      50                  55                  60

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser
  65                  70                  75                  80

Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn
                 85                  90                  95

Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
            100                 105                 110

Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser
        115                 120                 125

Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln
    130                 135                 140

Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys
145                 150                 155                 160

Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val
                165                 170                 175

Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr
            180                 185                 190

Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His
        195                 200                 205

Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His
    210                 215                 220

Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro
225                 230                 235                 240

Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
                245                 250                 255

Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser
            260                 265                 270

Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu
        275                 280                 285

Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg
    290                 295                 300

Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile
305                 310                 315                 320
```

```
Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys
                325                 330                 335

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys
            340                 345                 350

Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly
        355                 360                 365

Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu
    370                 375                 380

Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln
385                 390                 395                 400

Gln Gln Gln His Gln His Leu Leu Gln Lys His Leu Leu Ser Ala Cys
                405                 410                 415

Phe Arg Asn Glu Leu Val Glu Pro Arg Arg Glu Thr Pro Lys Gln Ser
            420                 425                 430

Asp Val Phe Phe Arg His Ser Lys Pro Pro Asn Arg Ser Val Tyr Pro
        435                 440                 445

<210> 341
<211> 356
<212> PRT
<213> Homo sapiens

<400> 341
Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
                5                  10                  15

Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn
            20                  25                  30

Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
        35                  40                  45

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
    50                  55                  60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
65                  70                  75                  80

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
                85                  90                  95

Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
            100                 105                 110

Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
        115                 120                 125
```

```
Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
    130                 135                 140

Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
145                 150                 155                 160

Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn
                165                 170                 175

Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
            180                 185                 190

Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val
        195                 200                 205

Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg
    210                 215                 220

Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val
225                 230                 235                 240

Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg
                245                 250                 255

Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
            260                 265                 270

Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Ser Arg Gln Asn Thr
        275                 280                 285

His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp
    290                 295                 300

Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu
305                 310                 315                 320

Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His
                325                 330                 335

Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu
            340                 345                 350

Leu Gln Lys Gln
        355
```

<210> 342
<211> 680
<212> PRT
<213> Homo sapiens

<400> 342

```
Met Asn Phe Glu Thr Ser Arg Cys Ala Thr Leu Gln Tyr Cys Pro Asp
                5                  10                  15
```

```
Pro Tyr Ile Gln Arg Phe Val Glu Thr Pro Ala His Phe Ser Trp Lys
            20                  25                  30

Glu Ser Tyr Tyr Arg Ser Thr Met Ser Gln Ser Thr Gln Thr Asn Glu
        35                  40                  45

Phe Leu Ser Pro Glu Val Phe Gln His Ile Trp Asp Phe Leu Glu Gln
    50                  55                  60

Pro Ile Cys Ser Val Gln Pro Ile Asp Leu Asn Phe Val Asp Glu Pro
65                  70                  75                  80

Ser Glu Asp Gly Ala Thr Asn Lys Ile Glu Ile Ser Met Asp Cys Ile
                85                  90                  95

Arg Met Gln Asp Ser Asp Leu Ser Asp Pro Met Trp Pro Gln Tyr Thr
            100                 105                 110

Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser
        115                 120                 125

Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser Val Thr
    130                 135                 140

Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala Leu Ser
145                 150                 155                 160

Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His Ser
                165                 170                 175

Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp
            180                 185                 190

Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr
        195                 200                 205

Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly Ala Val
    210                 215                 220

Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Glu Val
225                 230                 235                 240

Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn Glu Gly
                245                 250                 255

Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His
            260                 265                 270

Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val Leu Val
        275                 280                 285

Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val Leu Tyr
    290                 295                 300
```

```
Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro
305                 310                 315                 320

Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly
                325                 330                 335

Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg
            340                 345                 350

Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr
        355                 360                 365

Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr His Gly
    370                 375                 380

Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp Glu Leu
385                 390                 395                 400

Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys
                405                 410                 415

Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His Thr Ile
            420                 425                 430

Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu Leu Gln
        435                 440                 445

Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser Ser Pro
    450                 455                 460

Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val Ser Gln
465                 470                 475                 480

Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr Ile Pro
                485                 490                 495

Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met Pro Met
            500                 505                 510

Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro Pro Pro
        515                 520                 525

Leu Ser Met Pro Ser Thr Ser Gln Cys Thr Pro Pro Pro Pro Tyr Pro
    530                 535                 540

Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys Ser Ser
545                 550                 555                 560

Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr Gln Ile
                565                 570                 575

Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro Glu Gln
            580                 585                 590
```

```
Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln Leu His
        595                 600                 605

Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser Ala Ser
    610                 615                 620

Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val Ile Asp
625                 630                 635                 640

Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro Arg Asp
                645                 650                 655

Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn Lys Gln
            660                 665                 670

Gln Arg Ile Lys Glu Glu Gly Glu
        675                 680
```

Application Number 09/887,000

<200> 343
<211> 461
<212> PRT
<213> Homo sapiens

<400> 343

```
Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
                  5                  10                  15

Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn
             20                  25                  30

Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
         35                  40                  45

Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
     50                  55                  60

Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
 65                  70                  75                  80

His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
                 85                  90                  95

Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
            100                 105                 110

Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
        115                 120                 125

Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
    130                 135                 140

Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
145                 150                 155                 160
```

```
Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn
                165                 170                 175

Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
            180                 185                 190

Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val
        195                 200                 205

Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg
    210                 215                 220

Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val
225                 230                 235                 240

Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg
                245                 250                 255

Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
            260                 265                 270

Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr
        275                 280                 285

His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp
    290                 295                 300

Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu
305                 310                 315                 320

Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His
                325                 330                 335

Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu
            340                 345                 350

Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser
        355                 360                 365

Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val
    370                 375                 380

Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr
385                 390                 395                 400

Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met
                405                 410                 415

Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro
            420                 425                 430

Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro
        435                 440                 445
```

Tyr Pro Thr Asp Cys Ser Ile Val Arg Ile Trp Gln Val
450 455 460

<210> 344
<211> 516
<212> PRT
<213> Homo sapiens

<400> 344
Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe
5 10 15

Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
20 25 30

Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn
35 40 45

Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
50 55 60

Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser
65 70 75 80

Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn
85 90 95

Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
100 105 110

Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser
115 120 125

Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln
130 135 140

Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys
145 150 155 160

Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val
165 170 175

Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr
180 185 190

Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His
195 200 205

Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His
210 215 220

Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro
225 230 235 240

```
Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
                245                 250                 255

Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser
            260                 265                 270

Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu
        275                 280                 285

Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg
    290                 295                 300

Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile
305                 310                 315                 320

Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys
                325                 330                 335

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys
            340                 345                 350

Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly
        355                 360                 365

Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu
    370                 375                 380

Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln
385                 390                 395                 400

Gln Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser
                405                 410                 415

Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser
            420                 425                 430

Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg
        435                 440                 445

Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile
    450                 455                 460

Pro Met Met Gly Thr His Met Pro Met Ala Gly Asp Met Asn Gly Leu
465                 470                 475                 480

Ser Pro Thr Gln Ala Leu Pro Pro Pro Leu Ser Met Pro Ser Thr Ser
                485                 490                 495

His Cys Thr Pro Pro Pro Pro Tyr Pro Thr Asp Cys Ser Ile Val Arg
            500                 505                 510

Ile Trp Gln Val
        515
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<210> 345
<211> 1800
<212> DNA
<213> Homo sapiens

<400> 345
gcgcctcatt gccactgcag tgactaaagc tgggaagacg ctggtcagtt cacctgcccc 60
actggttgtt ttttaaacaa attctgatac aggcgacatc ctcactgacc gagcaaagat 120
tgacattcgt atcatcactg tgcaccattg gcttctaggc actccagtgg ggtaggagaa 180
ggaggtctga aaccctcgca gagggatctt gccctcattc tttgggtctg aaacactggc 240
agtcgttgga aacaggactc agggataaac cagcgcaatg gattggggga cgctgcacac 300
tttcatcggg ggtgtcaaca aacactccac cagcatcggg aaggtgtgga tcacagtcat 360
ctttattttc cgagtcatga tcctagtggt ggctgcccag gaagtgtggg gtgacgagca 420
agaggacttc gtctgcaaca cactgcaacc gggatgcaaa aatgtgtgct atgaccactt 480
tttcccggtg tcccacatcc ggctgtgggc cctccagctg atcttcgtct ccaccccagc 540
gctgctggtg gccatgcatg tggcctacta caggcacgaa accactcgca agttcaggcg 600
aggagagaag aggaatgatt tcaaagacat agaggacatt aaaaagcaca aggttcggat 660
agaggggtcg ctgtggtgga cgtacaccag cagcatcttt ttccgaatca tctttgaagc 720
agcctttatg tatgtgtttt acttccttta caatgggtac cacctgccct gggtgttgaa 780
atgtgggatt gacccctgcc ccaaccttgt tgactgcttt atttctaggc caacagagaa 840
gaccgtgttt accatttttа tgatttctgc gtctgtgatt tgcatgctgc ttaacgtggc 900
agagttgtgc tacctgctgc tgaaagtgtg ttttaggaga tcaaagagag cacagacgca 960
aaaaaatcac cccaatcatg ccctaaagga gagtaagcag aatgaaatga atgagctgat 1020
ttcagatagt ggtcaaaatg caatcacagg tttcccaagc taaacatttc aaggtaaaat 1080
gtagctgcgt cataaggaga cttctgtctt ctccagaagg caataccaac ctgaaagttc 1140
cttctgtagc ctgaagagtt tgtaaatgac tttcataata aatagacact tgagttaact 1200
ttttgtagga tacttgctcc attcatacac aacgtaatca aatatgtggt ccatctctga 1260
aaacaagaga ctgcttgaca aaggagcatt gcagtcactt tgacaggttc cttttaagtg 1320
gactctctga caaagtgggt actttctgaa aatttatata actgttgttg ataaggaaca 1380
tttatccagg aattgatacg tttattagga aaagatattt ttataggctt ggatgttttt 1440
agttccgact ttgaatttat ataaagtatt tttataatga ctggtcttcc ttacctggaa 1500
aaacatgcga tgttagtttt agaattacac cacaagtatc taaatttcca acttacaaag 1560
ggtcctatct tgtaaatatt gttttgcatt gtctgttggc aaatttgtga actgtcatga 1620
tacgcttaag gtgggaaagt gttcattgca caatatattt ttactgcttt ctgaatgtag 1680
acggaacagt gtggaagcag aaggcttttt taactcatcc gtttggccga tcgttgcaga 1740
ccactgggag atgtggatgt ggttgcctcc ttttgctcgt ccccgtggct taacccttct 1800

<210> 346
<211> 261
<212> PRT
<213> Homo sapiens

<400> 346
Met Asp Trp Gly Thr Leu His Thr Phe Ile Gly Gly Val Asn Lys His
1 5 10 15

Ser Thr Ser Ile Gly Lys Val Trp Ile Thr Val Ile Phe Ile Phe Arg
20 25 30

Val Met Ile Leu Val Val Ala Ala Gln Glu Val Trp Gly Asp Glu Gln

```
          35                  40                  45

Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
     50                  55                  60

Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln
 65                  70                  75                  80

Leu Ile Phe Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala
                 85                  90                  95

Tyr Tyr Arg His Glu Thr Thr Arg Lys Phe Arg Arg Gly Glu Lys Arg
            100                 105                 110

Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys His Lys Val Arg Ile
        115                 120                 125

Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Ile
    130                 135                 140

Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Phe Leu Tyr Asn Gly
145                 150                 155                 160

Tyr His Leu Pro Trp Val Leu Lys Cys Gly Ile Asp Pro Cys Pro Asn
                165                 170                 175

Leu Val Asp Cys Phe Ile Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
            180                 185                 190

Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala
        195                 200                 205

Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys Phe Arg Arg Ser Lys Arg
    210                 215                 220

Ala Gln Thr Gln Lys Asn His Pro Asn His Ala Leu Lys Glu Ser Lys
225                 230                 235                 240

Gln Asn Glu Met Asn Glu Leu Ile Ser Asp Ser Gly Gln Asn Ala Ile
                245                 250                 255

Thr Gly Phe Pro Ser
            260
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<210> 347
<211> 1740
<212> DNA
<213> Homo sapiens

<400> 347
atgaacaaac tgtatatcgg aaacctcagc gagaacgccg ccccctcgga cctagaaagt 60
atcttcaagg acgccaagat cccggtgtcg ggacccttcc tggtgaagac tggctacgcg 120

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ttcgtggact gcccggacga gagctgggcc ctcaaggcca tcgaggcgct ttcaggtaaa 180
atagaactgc acgggaaacc catagaagtt gagcactcgg tcccaaaaag gcaaaggatt 240
cggaaacttc agatacgaaa tatcccgcct catttacagt gggaggtgct ggatagttta 300
ctagtccagt atggagtggt ggagagctgt gagcaagtga acactgactc ggaaactgca 360
gttgtaaatg taacctattc cagtaaggac caagctagac aagcactaga caaactgaat 420
ggatttcagt tagagaattt caccttgaaa gtagcctata tccctgatga aacggccgcc 480
cagcaaaacc ccttgcagca gccccgaggt cgccgggggc ttgggcagag gggctcctca 540
aggcaggggt ctccaggatc cgtatccaag cagaaaccat gtgatttgcc tctgcgcctg 600
ctggttccca cccaatttgt tggagccatc ataggaaaag aaggtgccac cattcggaac 660
atcaccaaac agacccagtc taaaatcgat gtccaccgta aagaaaatgc gggggctgct 720
gagaagtcga ttactatcct ctctactcct gaaggcacct ctgcggcttg taagtctatt 780
ctggagatta tgcataagga agctcaagat ataaaattca cagaagagat ccccttgaag 840
attttagctc ataataactt tgttggacgt cttattggta aagaaggaag aaatcttaaa 900
aaaattgagc aagacacaga cactaaaatc acgatatctc cattgcagga attgacgctg 960
tataatccag aacgcactat tacagttaaa ggcaatgttg agacatgtgc caaagctgag 1020
gaggagatca tgaagaaaat cagggagtct tatgaaaatg atattgcttc tatgaatctt 1080
caagcacatt taattcctgg attaaatctg aacgccttgg gtctgttccc acccacttca 1140
gggatgccac ctcccacctc agggcccccc tcagccatga ctcctcccta cccgcagttt 1200
gagcaatcag aaacggagac tgttcatctg tttatcccag ctctatcagt cggtgccatc 1260
atcggcaagc agggccagca catcaagcag ctttctcgct ttgctggagc ttcaattaag 1320
attgctccag cggaagcacc agatgctaaa gtgaggatgg tgattatcac tggaccacca 1380
gaggctcagt tcaaggctca gggaagaatt tatggaaaaa ttaaagaaga aaactttgtt 1440
agtcctaaag aagaggtgaa acttgaagct catatcagag tgccatcctt tgctgctggc 1500
agagttattg gaaaaggagg caaaacggtg aatgaacttc agaatttgtc aagtgcagaa 1560
gttgttgtcc ctcgtgacca gacacctgat gagaatgacc aagtggttgt caaaataact 1620
ggtcacttct atgcttgcca ggttgcccag agaaaaattc aggaaattct gactcaggta 1680
aagcagcacc aacaacagaa ggctctgcaa agtggaccac ctcagtcaag acggaagtaa 1740
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<210> 348
<211> 579
<212> PRT
<213> Homo sapiens

<400> 348

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Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
                 5                  10                  15

Asp Leu Glu Ser Ile Phe Lys Asp Ala Lys Ile Pro Val Ser Gly Pro
             20                  25                  30

Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu Ser
         35                  40                  45

Trp Ala Leu Lys Ala Ile Glu Ala Leu Ser Gly Lys Ile Glu Leu His
     50                  55                  60

Gly Lys Pro Ile Glu Val Glu His Ser Val Pro Lys Arg Gln Arg Ile
 65                  70                  75                  80

Arg Lys Leu Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu Val
                 85                  90                  95

Leu Asp Ser Leu Leu Val Gln Tyr Gly Val Val Glu Ser Cys Glu Gln
```

```
                100                 105                 110

Val Asn Thr Asp Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Ser
        115                 120                 125

Lys Asp Gln Ala Arg Gln Ala Leu Asp Lys Leu Asn Gly Phe Gln Leu
    130                 135                 140

Glu Asn Phe Thr Leu Lys Val Ala Tyr Ile Pro Asp Glu Thr Ala Ala
145                 150                 155                 160

Gln Gln Asn Pro Leu Gln Gln Pro Arg Gly Arg Arg Gly Leu Gly Gln
                165                 170                 175

Arg Gly Ser Ser Arg Gln Gly Ser Pro Gly Ser Val Ser Lys Gln Lys
            180                 185                 190

Pro Cys Asp Leu Pro Leu Arg Leu Leu Val Pro Thr Gln Phe Val Gly
        195                 200                 205

Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln
    210                 215                 220

Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala
225                 230                 235                 240

Glu Lys Ser Ile Thr Ile Leu Ser Thr Pro Glu Gly Thr Ser Ala Ala
                245                 250                 255

Cys Lys Ser Ile Leu Glu Ile Met His Lys Glu Ala Gln Asp Ile Lys
            260                 265                 270

Phe Thr Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val
        275                 280                 285

Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu Gln
    290                 295                 300

Asp Thr Asp Thr Lys Ile Thr Ile Ser Pro Leu Gln Glu Leu Thr Leu
305                 310                 315                 320

Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Asn Val Glu Thr Cys
                325                 330                 335

Ala Lys Ala Glu Glu Glu Ile Met Lys Lys Ile Arg Glu Ser Tyr Glu
            340                 345                 350

Asn Asp Ile Ala Ser Met Asn Leu Gln Ala His Leu Ile Pro Gly Leu
        355                 360                 365

Asn Leu Asn Ala Leu Gly Leu Phe Pro Pro Thr Ser Gly Met Pro Pro
    370                 375                 380

Pro Thr Ser Gly Pro Pro Ser Ala Met Thr Pro Pro Tyr Pro Gln Phe
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385 390 395 400

Glu Gln Ser Glu Thr Glu Thr Val His Leu Phe Ile Pro Ala Leu Ser
405 410 415

Val Gly Ala Ile Ile Gly Lys Gln Gly Gln His Ile Lys Gln Leu Ser
420 425 430

Arg Phe Ala Gly Ala Ser Ile Lys Ile Ala Pro Ala Glu Ala Pro Asp
435 440 445

Ala Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe
450 455 460

Lys Ala Gln Gly Arg Ile Tyr Gly Lys Ile Lys Glu Glu Asn Phe Val
465 470 475 480

Ser Pro Lys Glu Glu Val Lys Leu Glu Ala His Ile Arg Val Pro Ser
485 490 495

Phe Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu
500 505 510

Leu Gln Asn Leu Ser Ser Ala Glu Val Val Val Pro Arg Asp Gln Thr
515 520 525

Pro Asp Glu Asn Asp Gln Val Val Val Lys Ile Thr Gly His Phe Tyr
530 535 540

Ala Cys Gln Val Ala Gln Arg Lys Ile Gln Glu Ile Leu Thr Gln Val
545 550 555 560

Lys Gln His Gln Gln Gln Lys Ala Leu Gln Ser Gly Pro Pro Gln Ser
565 570 575

Arg Arg Lys

<210> 349
<211> 207
<212> DNA
<213> Homo sapiens

<400> 349
atgtggcagc ccctcttctt caagtggctc ttgtcctgtt gccctgggag ttctcaaatt 60
gctgcagcag cctccaccca gcctgaggat gacatcaata cacagaggaa gaagagtcag 120
gaaaagatga gagaagttac agactctcct gggcgacccc gagagcttac cattcctcag 180
acttcttcac atggtgctaa cagattt 207

<210> 350
<211> 69
<212> PRT
<213> Homo sapiens

<400> 350
Met Trp Gln Pro Leu Phe Phe Lys Trp Leu Leu Ser Cys Cys Pro Gly
5 10 15

Ser Ser Gln Ile Ala Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp Ile
20 25 30

Asn Thr Gln Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val Thr Asp
35 40 45

Ser Pro Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr Ser Ser His
50 55 60

Gly Ala Asn Arg Phe
65

<210> 351
<211> 1012
<212> DNA
<213> Homo sapiens

<400> 351
ccctctagaa ataattttgt ttaactttaa gaaggagata tacatatgca tcaccatcac 60
catcacacgg ccgcgtccga taacttccag ctgtcccagg gtgggcaggg attcgccatt 120
ccgatcgggc aggcgatggc gatcgcgggc cagatcaagc ttcccaccgt tcatatcggg 180
cctaccgcct tcctcggctt gggtgttgtc gacaacaacg gcaacggcgc acgagtccaa 240
cgcgtggtcg ggagcgctcc ggcggcaagt ctcggcatct ccaccggcga cgtgatcacc 300
gcggtcgacg gcgctccgat caactcggcc accgcgatgg cggacgcgct taacgggcat 360
catcccggtg acgtcatctc ggtgacctgg caaaccaagt cgggcggcac gcgtacaggg 420
aacgtgacat tggccgaggg acccccggcc gaattcatgg attgggggac gctgcacact 480
ttcatcgggg gtgtcaacaa acactccacc agcatcggga aggtgtggat cacagtcatc 540
tttatttttcc gagtcatgat cctcgtggtg gctgcccagg aagtgtgggg tgacgagcaa 600
gaggacttcg tctgcaacac actgcaaccg ggatgcaaaa atgtgtgcta tgaccacttt 660
ttcccggtgt cccacatccg gctgtgggcc ctccagctga tcttcgtctc caccccagcg 720
ctgctggtgg ccatgcatgt ggcctactac aggcacgaaa ccactcgcaa gttcaggcga 780
ggagagaaga ggaatgattt caaagacata gaggacatta aaaagcagaa ggttcggata 840
gaggggtgac tcgagcacca ccaccaccac cactgagatc cggctgctaa caaagcccga 900
aaggaagctg agttggctgc tgccaccgct gagcaataac tagcataacc ccttggggcc 960
tctaaacggg tcttgagggg ttttttgctg aaaggaggaa ctatatccgg at 1012

<210> 352
<211> 267
<212> PRT
<213> Homo sapiens

<400> 352
Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
20 25 30

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Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
         35                  40                  45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
     50                  55                  60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
 65                  70                  75                  80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
                 85                  90                  95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
            100                 105                 110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
        115                 120                 125

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met Asp Trp Gly Thr Leu His
    130                 135                 140

Thr Phe Ile Gly Gly Val Asn Lys His Ser Thr Ser Ile Gly Lys Val
145                 150                 155                 160

Trp Ile Thr Val Ile Phe Ile Phe Arg Val Met Ile Leu Val Val Ala
                165                 170                 175

Ala Gln Glu Val Trp Gly Asp Glu Gln Glu Asp Phe Val Cys Asn Thr
            180                 185                 190

Leu Gln Pro Gly Cys Lys Asn Val Cys Tyr Asp His Phe Phe Pro Val
        195                 200                 205

Ser His Ile Arg Leu Trp Ala Leu Gln Leu Ile Phe Val Ser Thr Pro
    210                 215                 220

Ala Leu Leu Val Ala Met His Val Ala Tyr Tyr Arg His Glu Thr Thr
225                 230                 235                 240

Arg Lys Phe Arg Arg Gly Glu Lys Arg Asn Asp Phe Lys Asp Ile Glu
                245                 250                 255

Asp Ile Lys Lys Gln Lys Val Arg Ile Glu Gly
            260                 265
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<210> 353
<211> 900
<212> DNA
<213> Homo sapiens

<400> 353
atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60

cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120
accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgcacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcggtga cctggcaaac caagtcgggc 360
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt ccacgaaacc 420
actcgcaagt tcaggcgagg agagaagagg aatgatttca aagacataga ggacattaaa 480
aagcagaagg ttcggataga ggggtcgctg tggtggacgt acaccagcag catctttttc 540
cgaatcatct ttgaagcagc ctttatgtat gtgttttact tcctttacaa tgggtaccac 600
ctgccctggg tgttgaaatg tgggattgac ccctgcccca accttgttga ctgctttatt 660
tctaggccaa cagagaagac cgtgtttacc atttttatga tttctgcgtc tgtgatttgc 720
atgctgctta acgtggcaga gttgtgctac ctgctgctga aagtgtgttt taggagatca 780
aagagagcac agacgcaaaa aaatcacccc aatcatgccc taaaggagag taagcagaat 840
gaaatgaatg agctgatttc agatagtggt caaaatgcaa tcacaggttt cccaagctaa 900

<210> 354
<211> 299
<212> PRT
<213> Homo sapiens

<400> 354
Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
100 105 110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
115 120 125

Leu Ala Glu Gly Pro Pro Ala Glu Phe His Glu Thr Thr Arg Lys Phe
130 135 140

Arg Arg Gly Glu Lys Arg Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys
145 150 155 160

Lys Gln Lys Val Arg Ile Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser
165 170 175

Ser Ile Phe Phe Arg Ile Ile Phe Glu Ala Ala Phe Met Tyr Val Phe
180 185 190

Tyr Phe Leu Tyr Asn Gly Tyr His Leu Pro Trp Val Leu Lys Cys Gly
195 200 205

Ile Asp Pro Cys Pro Asn Leu Val Asp Cys Phe Ile Ser Arg Pro Thr
210 215 220

Glu Lys Thr Val Phe Thr Ile Phe Met Ile Ser Ala Ser Val Ile Cys
225 230 235 240

Met Leu Leu Asn Val Ala Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys
245 250 255

Phe Arg Arg Ser Lys Arg Ala Gln Thr Gln Lys Asn His Pro Asn His
260 265 270

Ala Leu Lys Glu Ser Lys Gln Asn Glu Met Asn Glu Leu Ile Ser Asp
275 280 285

Ser Gly Gln Asn Ala Ile Thr Gly Phe Pro Ser
290 295

<210> 355
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 355
ggagtacagc ttcaagacaa tggg 24

<210> 356
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 356
ccatgggaat tcattataat aattttgttc c 31

<210> 357
<211> 920
<212> PRT
<213> Homo sapiens

<400> 357
Met Gln His His His His His His Gly Val Gln Leu Gln Asp Asn Gly

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 1               5                  10                  15
Tyr Asn Gly Leu Leu Ile Ala Ile Asn Pro Gln Val Pro Glu Asn Gln
            20                  25                  30
Asn Leu Ile Ser Asn Ile Lys Glu Met Ile Thr Glu Ala Ser Phe Tyr
        35                  40                  45
Leu Phe Asn Ala Thr Lys Arg Arg Val Phe Phe Arg Asn Ile Lys Ile
    50                  55                  60
Leu Ile Pro Ala Thr Trp Lys Ala Asn Asn Asn Ser Lys Ile Lys Gln
65                  70                  75                  80
Glu Ser Tyr Glu Lys Ala Asn Val Ile Val Thr Asp Trp Tyr Gly Ala
                85                  90                  95
His Gly Asp Asp Pro Tyr Thr Leu Gln Tyr Arg Gly Cys Gly Lys Glu
            100                 105                 110
Gly Lys Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Asn Asp Asn Leu
        115                 120                 125
Thr Ala Gly Tyr Gly Ser Arg Gly Arg Val Phe Val His Glu Trp Ala
    130                 135                 140
His Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Asn Asp Lys Pro Phe
145                 150                 155                 160
Tyr Ile Asn Gly Gln Asn Gln Ile Lys Val Thr Arg Cys Ser Ser Asp
                165                 170                 175
Ile Thr Gly Ile Phe Val Cys Glu Lys Gly Pro Cys Pro Gln Glu Asn
            180                 185                 190
Cys Ile Ile Ser Lys Leu Phe Lys Glu Gly Cys Thr Phe Ile Tyr Asn
        195                 200                 205
Ser Thr Gln Asn Ala Thr Ala Ser Ile Met Phe Met Gln Ser Leu Ser
    210                 215                 220
Ser Val Val Glu Phe Cys Asn Ala Ser Thr His Asn Gln Glu Ala Pro
225                 230                 235                 240
Asn Leu Gln Asn Gln Met Cys Ser Leu Arg Ser Ala Trp Asp Val Ile
                245                 250                 255
Thr Asp Ser Ala Asp Phe His His Ser Phe Pro Met Asn Gly Thr Glu
            260                 265                 270
Leu Pro Pro Pro Pro Thr Phe Ser Leu Val Glu Ala Gly Asp Lys Val
        275                 280                 285
Val Cys Leu Val Leu Asp Val Ser Ser Lys Met Ala Glu Ala Asp Arg
    290                 295                 300
Leu Leu Gln Leu Gln Gln Ala Ala Glu Phe Tyr Leu Met Gln Ile Val
305                 310                 315                 320
Glu Ile His Thr Phe Val Gly Ile Ala Ser Phe Asp Ser Lys Gly Glu
                325                 330                 335
Ile Arg Ala Gln Leu His Gln Ile Asn Ser Asn Asp Asp Arg Lys Leu
            340                 345                 350
Leu Val Ser Tyr Leu Pro Thr Thr Val Ser Ala Lys Thr Asp Ile Ser
        355                 360                 365
Ile Cys Ser Gly Leu Lys Lys Gly Phe Glu Val Val Glu Lys Leu Asn
    370                 375                 380
Gly Lys Ala Tyr Gly Ser Val Met Ile Leu Val Thr Ser Gly Asp Asp
385                 390                 395                 400
Lys Leu Leu Gly Asn Cys Leu Pro Thr Val Leu Ser Ser Gly Ser Thr
                405                 410                 415
Ile His Ser Ile Ala Leu Gly Ser Ser Ala Ala Pro Asn Leu Glu Glu
            420                 425                 430
Leu Ser Arg Leu Thr Gly Gly Leu Lys Phe Phe Val Pro Asp Ile Ser
```

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         435                 440                 445
Asn Ser Asn Ser Met Ile Asp Ala Phe Ser Arg Ile Ser Ser Gly Thr
    450                 455                 460
Gly Asp Ile Phe Gln Gln His Ile Gln Leu Glu Ser Thr Gly Glu Asn
465                 470                 475                 480
Val Lys Pro His His Gln Leu Lys Asn Thr Val Thr Val Asp Asn Thr
                485                 490                 495
Val Gly Asn Asp Thr Met Phe Leu Val Thr Trp Gln Ala Ser Gly Pro
            500                 505                 510
Pro Glu Ile Ile Leu Phe Asp Pro Asp Gly Arg Lys Tyr Tyr Thr Asn
        515                 520                 525
Asn Phe Ile Thr Asn Leu Thr Phe Arg Thr Ala Ser Leu Trp Ile Pro
    530                 535                 540
Gly Thr Ala Lys Pro Gly His Trp Thr Tyr Thr Leu Asn Asn Thr His
545                 550                 555                 560
His Ser Leu Gln Ala Leu Lys Val Thr Val Thr Ser Arg Ala Ser Asn
                565                 570                 575
Ser Ala Val Pro Pro Ala Thr Val Glu Ala Phe Val Glu Arg Asp Ser
            580                 585                 590
Leu His Phe Pro His Pro Val Met Ile Tyr Ala Asn Val Lys Gln Gly
        595                 600                 605
Phe Tyr Pro Ile Leu Asn Ala Thr Val Thr Ala Thr Val Glu Pro Glu
    610                 615                 620
Thr Gly Asp Pro Val Thr Leu Arg Leu Leu Asp Asp Gly Ala Gly Ala
625                 630                 635                 640
Asp Val Ile Lys Asn Asp Gly Ile Tyr Ser Arg Tyr Phe Phe Ser Phe
                645                 650                 655
Ala Ala Asn Gly Arg Tyr Ser Leu Lys Val His Val Asn His Ser Pro
            660                 665                 670
Ser Ile Ser Thr Pro Ala His Ser Ile Pro Gly Ser His Ala Met Tyr
        675                 680                 685
Val Pro Gly Tyr Thr Ala Asn Gly Asn Ile Gln Met Asn Ala Pro Arg
    690                 695                 700
Lys Ser Val Gly Arg Asn Glu Glu Glu Arg Lys Trp Gly Phe Ser Arg
705                 710                 715                 720
Val Ser Ser Gly Gly Ser Phe Ser Val Leu Gly Val Pro Ala Gly Pro
                725                 730                 735
His Pro Asp Val Phe Pro Pro Cys Lys Ile Ile Asp Leu Glu Ala Val
            740                 745                 750
Lys Val Glu Glu Glu Leu Thr Leu Ser Trp Thr Ala Pro Gly Glu Asp
        755                 760                 765
Phe Asp Gln Gly Gln Ala Thr Ser Tyr Glu Ile Arg Met Ser Lys Ser
    770                 775                 780
Leu Gln Asn Ile Gln Asp Asp Phe Asn Asn Ala Ile Leu Val Asn Thr
785                 790                 795                 800
Ser Lys Arg Asn Pro Gln Gln Ala Gly Ile Arg Glu Ile Phe Thr Phe
                805                 810                 815
Ser Pro Gln Ile Ser Thr Asn Gly Pro Glu His Gln Pro Asn Gly Glu
            820                 825                 830
Thr His Glu Ser His Arg Ile Tyr Val Ala Ile Arg Ala Met Asp Arg
        835                 840                 845
Asn Ser Leu Gln Ser Ala Val Ser Asn Ile Ala Gln Ala Pro Leu Phe
    850                 855                 860
Ile Pro Pro Asn Ser Asp Pro Val Pro Ala Arg Asp Tyr Leu Ile Leu
```

```
865                 870                 875                 880
Lys Gly Val Leu Thr Ala Met Gly Leu Ile Gly Ile Ile Cys Leu Ile
                885                 890                 895
Ile Val Val Thr His His Thr Leu Ser Arg Lys Lys Arg Ala Asp Lys
            900                 905                 910
Lys Glu Asn Gly Thr Lys Leu Leu
        915                 920
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<210> 358
<211> 2773
<212> DNA
<213> Homo sapiens

<400> 358

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catatgcagc atcaccacca tcaccacgga gtacagcttc aagacaatgg gtataatgga      60
ttgctcattg caattaatcc tcaggtacct gagaatcaga acctcatctc aaacattaag     120
gaaatgataa ctgaagcttc attttaccta tttaatgcta ccaagagaag agtatttttc     180
agaaatataa agattttaat acctgccaca tggaaagcta ataataacag caaaataaaa     240
caagaatcat atgaaaaggc aaatgtcata gtgactgact ggtatggggc acatggagat     300
gatccataca ccctacaata cagagggtgt ggaaaagagg gaaaatacat tcatttcaca     360
cctaatttcc tactgaatga taacttaaca gctggctacg gatcacgagg ccgagtgttt     420
gtccatgaat gggcccacct ccgttggggt gtgttcgatg agtataacaa tgacaaacct     480
ttctacataa atgggcaaaa tcaaattaaa gtgacaaggt gttcatctga catcacaggc     540
atttttgtgt gtgaaaaagg tccttgcccc caagaaaact gtattattag taagcttttt     600
aaagaaggat gcacctttat ctacaatagc acccaaaatg caactgcatc aataatgttc     660
atgcaaagtt tatcttctgt ggttgaattt tgtaatgcaa gtacccacaa ccaagaagca     720
ccaaacctac agaaccagat gtgcagcctc agaagtgcat gggatgtaat cacagactct     780
gctgactttc accacagctt tcccatgaac gggactgagc ttccacctcc tcccacattc     840
tcgcttgtag aggctggtga caaagtggtc tgtttagtgc tggatgtgtc cagcaagatg     900
gcagaggctg acagactcct tcaactacaa caagccgcag aattttattt gatgcagatt     960
gttgaaattc ataccttcgt gggcattgcc agtttcgaca gcaaaggaga gatcagagcc    1020
cagctacacc aaattaacag caatgatgat cgaaagttgc tggtttcata tctgcccacc    1080
actgtatcag ctaaaacaga catcagcatt tgttcagggc ttaagaaagg atttgaggtg    1140
gttgaaaaac tgaatggaaa agcttatggc tctgtgatga tattagtgac cagcggagat    1200
gataagcttc ttggcaattg cttacccact gtgctcagca gtggttcaac aattcactcc    1260
attgccctgg gttcatctgc agccccaaat ctggaggaat tatcacgtct tacaggaggt    1320
ttaaagttct ttgttccaga tatatcaaac tccaatagca tgattgatgc tttcagtaga    1380
atttcctctg gaactggaga cattttccag caacatattc agcttgaaag tacaggtgaa    1440
aatgtcaaac ctcaccatca attgaaaaac acagtgactg tggataatac tgtgggcaac    1500
gacactatgt ttctagttac gtggcaggcc agtggtcctc ctgagattat attatttgat    1560
cctgatggac gaaaatacta cacaaataat tttatcacca atctaacttt tcggacagct    1620
agtctttgga ttccaggaac agctaagcct gggcactgga cttacaccct gaacaatacc    1680
catcattctc tgcaagccct gaaagtgaca gtgacctctc gcgcctccaa ctcagctgtg    1740
cccccagcca ctgtggaagc ctttgtggaa agagacagcc tccattttcc tcatcctgtg    1800
atgatttatg ccaatgtgaa acagggattt tatcccattc ttaatgccac tgtcactgcc    1860
acagttgagc cagagactgg agatcctgtt acgctgagac tccttgatga tggagcaggt    1920
gctgatgtta taaaaaatga tggaatttac tcgaggtatt ttttctcctt tgctgcaaat    1980
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ctatcttgga cagcacctgg agaagacttt gatcagggcc aggctacaag ctatgaaata    2340
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acatcaaagc gaaatcctca gcaagctggc atcagggaga tatttacgtt ctcaccccaa 2460
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<210> 359
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 359
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<210> 360
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 360
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<210> 361
<211> 77
<212> PRT
<213> Homo sapiens

<400> 361
Met Gln His His His His His His Trp Gln Pro Leu Phe Phe Lys Trp
 1   5   10   15
Leu Leu Ser Cys Cys Pro Gly Ser Ser Gln Ile Ala Ala Ala Ala Ser
            20   25   30
Thr Gln Pro Glu Asp Asp Ile Asn Thr Gln Arg Lys Lys Ser Gln Glu
        35   40   45
Lys Met Arg Glu Val Thr Asp Ser Pro Gly Arg Pro Arg Glu Leu Thr
    50   55   60
Ile Pro Gln Thr Ser Ser His Gly Ala Asn Arg Phe Val
65   70   75

<210> 362
<211> 244
<212> DNA
<213> Homo sapiens

<400> 362
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aatacacaga ggaagaagag tcaggaaaag atgagagaag ttacagactc tcctgggcga 180
ccccgagagc ttaccattcc tcagacttct tcacatggtg ctaacagatt tgtttgatga 240
attc 244

<210> 363
<211> 20
<212> PRT
<213> Homo sapiens

<400> 363
Met Trp Gln Pro Leu Phe Phe Lys Trp Leu Leu Ser Cys Cys Pro Gly
5 10 15
Ser Ser Gln Ile
20

<210> 364
<211> 60
<212> DNA
<213> Homo sapiens

<400> 364
atgtggcagc ccctcttctt caagtggctc ttgtcctgtt gccctgggag ttctcaaatt 60

<210> 365
<211> 20
<212> PRT
<213> Homo sapiens

<400> 365
Gly Ser Ser Gln Ile Ala Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp
5 10 15
Ile Asn Thr Gln
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<210> 366
<211> 60
<212> DNA
<213> Homo sapiens

<400> 366
gggagttctc aaattgctgc agcagcctcc acccagcctg aggatgacat caatacacag 60

<210> 367
<211> 20
<212> PRT
<213> Homo sapiens

<400> 367
Lys Pro Gly His Trp Thr Tyr Thr Leu Asn Asn Thr His His Ser Leu
5 10 15
Gln Ala Leu Lys

20

<210> 368
<211> 2343
<212> DNA
<213> Homo sapiens

<400> 368
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gcgccgcgcc tctgaggcgc agcatgtgaa gcggagacgg catccagtgg ggggcgagcc 180
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gaatatattg aacgtcttgt atggagaacc ccaggaggag gctctagagg tggacctgaa 300
gcttttgatc ctaaaagatt attagaagaa tttgtaaatc atattcagga actccagata 360
atggatgaaa ggattcagag gaaagtagag aaactagagc aacaatgtca gaaagaagcc 420
aaggaatttg ccaagaaggt acaagagctg cagaaaagca atcaggttgc cttccaacat 480
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tactttaatg agtttctaga tggagaattg aaatctgatg tttttacaaa ttctgaaaag 660
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gatagatttt cagaagttaa atccaaaatt gcaagtaaat accatgattt agaatgccag 780
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<210> 369
<211> 708
<212> PRT
<213> Homo sapiens

<400> 369

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            20                  25                  30
Gly Pro Glu Ala Phe Asp Pro Lys Arg Leu Leu Glu Glu Phe Val Asn
        35                  40                  45
His Ile Gln Glu Leu Gln Ile Met Asp Glu Arg Ile Gln Arg Lys Val
    50                  55                  60
Glu Lys Leu Glu Gln Gln Cys Gln Lys Glu Ala Lys Glu Phe Ala Lys
65                  70                  75                  80
Lys Val Gln Glu Leu Gln Lys Ser Asn Gln Val Ala Phe Gln His Phe
                85                  90                  95
Gln Glu Leu Asp Glu His Ile Ser Tyr Val Ala Thr Lys Val Cys His
            100                 105                 110
Leu Gly Asp Gln Leu Glu Gly Val Asn Thr Pro Arg Gln Arg Ala Val
        115                 120                 125
Glu Ala Gln Lys Leu Met Lys Tyr Phe Asn Glu Phe Leu Asp Gly Glu
    130                 135                 140
Leu Lys Ser Asp Val Phe Thr Asn Ser Glu Lys Ile Lys Glu Ala Ala
145                 150                 155                 160
Asp Ile Ile Gln Lys Leu His Leu Ile Ala Gln Glu Leu Pro Phe Asp
                165                 170                 175
Arg Phe Ser Glu Val Lys Ser Lys Ile Ala Ser Lys Tyr His Asp Leu
            180                 185                 190
Glu Cys Gln Leu Ile Gln Glu Phe Thr Ser Ala Gln Arg Arg Gly Glu
        195                 200                 205
Ile Ser Arg Met Arg Glu Val Ala Ala Val Leu Leu His Phe Lys Gly
    210                 215                 220
Tyr Ser His Cys Val Asp Val Tyr Ile Lys Gln Cys Gln Glu Gly Ala
225                 230                 235                 240
Tyr Leu Arg Asn Asp Ile Phe Glu Asp Ala Gly Ile Leu Cys Gln Arg
                245                 250                 255
Val Asn Lys Gln Val Gly Asp Ile Phe Ser Asn Pro Glu Thr Val Leu
            260                 265                 270
Ala Lys Leu Ile Gln Asn Val Phe Glu Ile Lys Leu Gln Ser Phe Val
        275                 280                 285
Lys Glu Gln Leu Glu Glu Cys Arg Lys Ser Asp Ala Glu Gln Tyr Leu
    290                 295                 300
Lys Asn Leu Tyr Asp Leu Tyr Thr Arg Thr Thr Asn Leu Ser Ser Lys
305                 310                 315                 320
Leu Met Glu Phe Asn Leu Gly Thr Asp Lys Gln Thr Phe Leu Ser Lys
                325                 330                 335
Leu Ile Lys Ser Ile Phe Ile Ser Tyr Leu Glu Asn Tyr Ile Glu Val
            340                 345                 350
Glu Thr Gly Tyr Leu Lys Ser Arg Ser Ala Met Ile Leu Gln Arg Tyr
        355                 360                 365
Tyr Asp Ser Lys Asn His Gln Lys Arg Ser Ile Gly Thr Gly Gly Ile
    370                 375                 380
Gln Asp Leu Lys Glu Arg Ile Arg Gln Arg Thr Asn Leu Pro Leu Gly
385                 390                 395                 400
Pro Ser Ile Asp Thr His Gly Glu Thr Phe Leu Ser Gln Glu Val Val
                405                 410                 415
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Val Asn Leu Leu Gln Glu Thr Lys Gln Ala Phe Glu Arg Cys His Arg
            420                 425                 430
Leu Ser Asp Pro Ser Asp Leu Pro Arg Asn Ala Phe Arg Ile Phe Thr
        435                 440                 445
Ile Leu Val Glu Phe Leu Cys Ile Glu His Ile Asp Tyr Ala Leu Glu
    450                 455                 460
Thr Gly Leu Ala Gly Ile Pro Ser Ser Asp Ser Arg Asn Ala Asn Leu
465                 470                 475                 480
Tyr Phe Leu Asp Val Val Gln Gln Ala Asn Thr Ile Phe His Leu Phe
                485                 490                 495
Asp Lys Gln Phe Asn Asp His Leu Met Pro Leu Ile Ser Ser Ser Pro
            500                 505                 510
Lys Leu Ser Glu Cys Leu Gln Lys Lys Lys Glu Ile Ile Glu Gln Met
        515                 520                 525
Glu Met Lys Leu Asp Thr Gly Ile Asp Arg Thr Leu Asn Cys Met Ile
    530                 535                 540
Gly Gln Met Lys His Ile Leu Ala Ala Glu Gln Lys Lys Thr Asp Phe
545                 550                 555                 560
Lys Pro Glu Asp Glu Asn Asn Val Leu Ile Gln Tyr Thr Asn Ala Cys
                565                 570                 575
Val Lys Val Cys Ala Tyr Val Arg Lys Gln Val Glu Lys Ile Lys Asn
            580                 585                 590
Ser Met Asp Gly Lys Asn Val Asp Thr Val Leu Met Glu Leu Gly Val
        595                 600                 605
Arg Phe His Arg Leu Ile Tyr Glu His Leu Gln Gln Tyr Ser Tyr Ser
    610                 615                 620
Cys Met Gly Gly Met Leu Ala Ile Cys Asp Val Ala Glu Tyr Arg Lys
625                 630                 635                 640
Cys Ala Lys Asp Phe Lys Ile Pro Met Val Leu His Leu Phe Asp Thr
                645                 650                 655
Leu His Ala Leu Cys Asn Leu Leu Val Val Ala Pro Asp Asn Leu Lys
            660                 665                 670
Gln Val Cys Ser Gly Glu Gln Leu Ala Asn Leu Asp Lys Asn Ile Leu
        675                 680                 685
His Ser Phe Val Gln Leu Arg Ala Asp Tyr Arg Ser Ala Arg Leu Ala
    690                 695                 700
Arg His Phe Ser
705
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<210> 370
<211> 60
<212> DNA
<213> Homo sapiens

<400> 370
gtcaatcact ctcccagcat aagcacccca gcccactcta ttccagggag tcatgctatg 60

<210> 371
<211> 60
<212> DNA
<213> Homo sapiens

<400> 371
agtagaattt cctctggaac tggagacatt ttccagcaac atattcagct tgaaagtaca 60

<210> 372
<211> 60
<212> DNA
<213> Homo sapiens

<400> 372
ccagagactg gagatcctgt tacgctgaga ctccttgatg atggagcagg tgctgatgtt 60

<210> 373
<211> 60
<212> DNA
<213> Homo sapiens

<400> 373
ttacagtctg ctgtatctaa cattgcccag gcgcctctgt ttattccccc caattctgat 60

<210> 374
<211> 60
<212> DNA
<213> Homo sapiens

<400> 374
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<210> 375
<211> 60
<212> DNA
<213> Homo sapiens

<400> 375
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<210> 376
<211> 20
<212> PRT
<213> Homo sapiens

<400> 376
Leu Gln Ser Ala Val Ser Asn Ile Ala Gln Ala Pro Leu Phe Ile Pro
1 5 10 15

Pro Asn Ser Asp
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<210> 377
<211> 20
<212> PRT
<213> Homo sapiens

<400> 377
Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile Pro Gly
5 10 15

Ser His Ala Met
20

<210> 378
<211> 20
<212> PRT
<213> Homo sapiens

<400> 378
Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu Leu Asp Asp Gly Ala
5 10 15

Gly Ala Asp Val
20

<210> 379
<211> 20
<212> PRT
<213> Homo sapiens

<400> 379
Ala Val Pro Pro Ala Thr Val Glu Ala Phe Val Glu Arg Asp Ser Leu
5 10 15

His Phe Pro His
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<210> 380
<211> 20
<212> PRT
<213> Homo sapiens

<400> 380
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
5 10 15

Leu Glu Ser Thr
20

<210> 381
<211> 20
<212> PRT
<213> Homo sapiens

<400> 381
Lys Asn Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe

5 10 15

Leu Val Thr Trp
20